Université de Montréal

# Neurocognitive Basis of Aggressive Behaviors in Schizophrenia

*A Neuroimaging Study*

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**Neurocognitive Basis of Aggressive Behaviors in Schizophrenia**
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*Présenté par*
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*A été évalué(e) par un jury composé des personnes suivantes*

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# Résumé

Bien que les individus atteints de schizophrénie présentent un risque élevé de manifester des comportements agressifs par rapport à la population générale, peu d'efforts ont été consacrés à élucider les mécanismes neurocognitifs sous-jacents à cette augmentation. L'objectif de cette thèse était d'étudier les processus susceptibles d'être perturbés dans cette population spécifique de patients, notamment le traitement des émotions, le contrôle cognitif et le traitement de la récompense. À cette fin, nous avons eu recours à l'imagerie par résonance magnétique fonctionnelle basée sur des tâches, à de grands échantillons et à des groupes de contrôle appropriés de patients et de non-patients.

Dans le premier échantillon de participants, nous avons évalué les altérations neurofonctionnelles chez des hommes souffrant de schizophrénie et ayant des antécédents de comportements agressifs en utilisant une tâche de traitement des émotions basée sur des images émotionnelles standardisées. Dans la première étude, les hommes violents atteints de schizophrénie ont montré une augmentation de la réponse du cortex cingulaire antérieur (ACC) aux images négatives, contrairement aux sujets sains et schizophrènes non-violents. La deuxième étude a approfondi ces résultats en identifiant une topologie perturbée de connectivité fonctionnelle basée sur la tâche au sein du réseau de la saillance émotionnelle pendant le traitement des émotions negatives. Ceci suggère une intégration inefficace des informations par l'ACC entre les régions frontales et limbiques. Ensemble, ces résultats soulignent l'importance de l'ACC dans la neurobiologie des comportements agressifs dans la schizophrénie.

Dans le deuxième échantillon de participants, nous avons évalué le contrôle cognitif et le traitement de la récompense dans l'agression. Dans la troisième étude, nous avons examiné

l'interaction entre le traitement des émotions négatives et le contrôle cognitif chez les hommes atteints de schizophrénie et ayant des antécédents de violence en emplyant une tâche Go-NoGo émotionnelle utilisant des stimuli de visages neutres et en colère. Nous avons constaté une activation réduite dans le cortex préfrontal dorsolatéral chez les hommes violents atteints de schizophrénie, en particulier lorsqu'ils inhibaient une réponse en regardant des visages en colère. Ces résultats indiquent une incapacité à recruter une région centrale du réseau de contrôle cognitif dans le contexte de la colère. Dans la quatrième étude, nous avons cherché à investiguer l'altération de la prise de décision liée à la récompense et son association avec l'agressivité dans la schizophrénie en utilisant le Balloon Analogue Risk Task. La tâche n'a pas fait ressortir de différences entre les hommes violents et non violents atteints de schizophrénie. Néanmoins, nous avons observé des activations plus élevées dans le striatum et l'insula en réponse à des événements de récompense, suggérant potentiellement que la surévaluation des stimuli de récompense peut être à la base des capacités de prise de décision altérées des individus atteints de schizophrénie.

Cette thèse est la première à identifier des altérations de l'activité cérébrale fonctionnelle et de la connectivité pendant le traitement des émotions négatives chez des hommes agressifs atteints de schizophrénie. C'est également la première à observer des mécanismes neuronaux altérés impliqués dans l'interaction entre le contrôle cognitif et le traitement de la colère chez des hommes violents atteints de schizophrénie.

**Mots-clés:** Schizophrénie, violence, agression, émotions négatives, récompense, contrôle cognitif, prise de décision, IRM, IRMf

# Abstract

Despite individuals with schizophrenia being at an elevated risk for aggressive behaviors compared to the general population, limited efforts have been devoted to understanding the neurocognitive mechanisms underlying the increase. The objective of this dissertation was to investigate processes thought to be disrupted in this specific patient population including emotion processing, cognitive control, and reward processing. To this end, we utilized task-based functional magnetic resonance imaging, large samples, and appropriate patient and non-patient control groups.

In the first sample of participants, we assessed neurofunctional alterations in men with schizophrenia and a history of aggressive behaviors using an emotional processing task based on standardized affective photographs. In the first study, violent men with schizophrenia displayed increased anterior cingular cortex (ACC) response to negative images as opposed to non-violent healthy individuals and individuals with schizophrenia. The second study expanded on these results by identifying disrupted task-based functional connectivity topology within the emotional-salience network during negative emotion processing suggestive of inefficient information integration by the ACC between frontal and limbic regions. Together, these highlight the importance of the ACC in the neurobiology of aggressive behaviors in schizophrenia.

In the second sample of participants, we assessed cognitive control and reward processing in aggression. In the third study, we investigated the interaction between negative emotion processing and inhibitory control among men with schizophrenia and a history of violence by employing an affective Go-NoGo task utilizing angry and neutral face stimuli. We found a reduced activation in the dorsolateral prefrontal cortex in violent men with

schizophrenia specifically when inhibiting a response while viewing angry faces. These results are indicative of an inability to recruit a core region of the cognitive control network in the context of anger. In the fourth study, we aimed to investigate impaired reward-related decision-making and its association with aggression in schizophrenia using the Balloon Analogue Risk Task. The task did not elicit differences between violent and non-violent men with schizophrenia. Nevertheless, we observed increased activations in the striatum and insula in response to reward events potentially suggesting that overvaluation of outcome stimuli may underlie the impaired decision-making abilities of individuals with schizophrenia.

This dissertation is the first to identify alterations in functional brain activity and connectivity during the processing of negative emotions among aggressive men with schizophrenia. This is also the first to observe impaired neural mechanisms involved in the interaction between cognitive control and anger processing among violent men with schizophrenia.

**Keywords:** Schizophrenia, violence, aggression, negative emotions, reward, cognitive control, decision-making, MRI, fMRI

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# List of acronyms and abbreviations

ACC : Anterior cingulate cortex
aINS : Anterior insula
ASPD : Antisocial personality disorder
CBT : Cognitive behavioral therapy
CD : Conduct disorder
CRT : Cognitive remediation therapy
dACC : Dorsal anterior cingulate cortex
DLPFC : Dorsolateral prefrontal cortex
DMOFC : Dorsomedial orbitofrontal cortex
DSM : Diagnostic and statistical manual of mental disorders
DUNDRUM : Dangerousness, understanding, recovery and urgency manual
fMRI : Functional magnetic resonance imaging
HC : Hippocampus
HCR-20 : Historical clinical risk management-20
HPA : Hypothalamic–pituitary–adrenal
IQ : Intelligence quotient
MBC : Measurement based care
MPFC : Medial prefrontal cortex
MRI : Magnetic resonance imaging
NIMH : National institute of mental health
NMDA : N-methyl-d-aspartate
OFC : Orbitofrontal cortex
OMPFC : Orbitomedial prefrontal cortex
PET : Positron emission tomography
PFC : Prefrontal cortex
rACC : Rostral anterior cingulate cortex
SCZ+V : Violent individuals with schizophrenia
VLPFC : Ventrolateral prefrontal cortex
VMPFC : Ventromedial prefrontal cortex
VRAG : Violence risk appraisal guide

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# 1 Introduction

## 1.1 Schizophrenia

Schizophrenia is a serious, chronic, debilitating psychiatric illness, with a worldwide lifetime prevalence estimated to range between 0.34%-0.85% (Simeone et al., 2015). The severe psychiatric disorder has detrimental consequences for patients and their families (Andreasen, 2010), and represents a significant societal burden in term of the care required (Jin & Mosweu, 2017). This is especially apparent when contrasting the relative occurrence of the disease to the costs associated with healthcare and productivity loss, as they were appraised to be 1.7% of national healthcare expenditure in Canada (Goeree et al., 2005) and up to 1.65% of the gross domestic product in countries worldwide (Chong et al., 2016).

Schizophrenia has a high mortality rate, with 14.5 years of potential life lost on average (Hjorthoj et al., 2017). A significant portion is attributable to higher incidence rates of comorbid physical disorders in individuals with schizophrenia as compared to the general population, including cancers (e.g., leukemia, tumors of any origin), metabolic disorders (e.g., diabetes mellitus type I and II), brain disorders (e.g., dementia, hemiplegia, cerebrovascular disease), cardiovascular disorders (e.g., peripheral vascular disease, congestive heart failure, myocardial infarction), infections (e.g., acquired immunodeficiency syndrome) and chronic pulmonary diseases (Laursen, Munk-Olsen & Gasse, 2011). Their increased occurrence in this population has been associated in part to factors such as antipsychotic medication, smoking, decreased physical activity, and poor dietary habits (Laursen, Nordentoft & Mortensen, 2014; Pack, 2009). A high rate of suicide, approximately 5% lifetime risk for completed (Hor & Taylor, 2010) and

>25% lifetime prevalence for attempted suicide (Lu et al., 2020), is a major contributor to the excess mortality observed in this patient population.

The current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association (2013c)) details a list of schizophrenia spectrum disorders, including schizotypal personality disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, and substance induced psychotic disorder. Schizophrenia is a heterogenous clinical diagnosis established based on symptoms divided into diagnostic criteria (A-D), which include A) 5 symptom domains, necessitating the presence of 2 or more during a period of at least 1 month for a diagnosis, including *i)* delusions (i.e., fixed false idea or beliefs), *ii)* hallucinations (i.e., perceptions without corresponding external stimuli), *iii)* disorganized speech (e.g., loose associations, incoherence), *iv)* grossly disorganized or catatonic behavior (e.g., agitation or decreased reactivity), and *v)* negative symptoms (i.e., blunted affect, avolition, alogia, anhedonia, asociality). The symptoms should impact the B) level of functioning (e.g., work, relationships, self-care, academia), and C) signs of disturbances should persist for at least 6 months. Finally, D) symptoms should not be explainable by substance use or other medical conditions (e.g., stroke, dementia, Parkinson's disease, Alzheimer's disease). Schizophrenia is predominantly diagnosed in late adolescence/early adulthood, with earlier age of onset being associated with poorer functional outcome (Immonen et al., 2017) and higher rate of developing brain abnormalities (Hollis & Rapoport, 2011). The prognosis of the disorder is relatively guarded (an der Heiden & Häfner, 2000). A chronic course of illness is reported in approximately 2/3 of diagnosed individuals, of whom half deteriorate versus half stabilize (an der Heiden & Häfner,

2010). Recovery is observed in less than 1/3 of individuals with schizophrenia (Jääskeläinen et al., 2013; Lally et al., 2017).

From a diagnostic perspective, schizophrenia is primarily defined by the presence and duration of psychosis, which is a state of impaired reality-testing, and associated cluster of symptoms (i.e., delusions, hallucinations, disorganized speech and behavior) (Freudenreich, Brown & Holt, 2015). These positive symptoms (i.e., exaggeration of normal processes) are emphasized in the criteria and predict a higher risk of hospitalization in first episode psychosis (Robinson et al., 2019) as well as in adult individuals with schizophrenia (Glick, Li & Harvey, 2015). Conversely, negative symptoms (i.e., diminution or negation of normal processes) and cognitive symptoms are core features of the syndrome contributing to psychosocial disability (Arango & Carpenter, 2011; Freudenreich et al., 2015). Deficits of 0.5 to 1.5 standard deviations below healthy control were reported in premorbid cognitive scores (Keefe, 2014). Cognitive impairment was also found to be a risk factor for schizophrenia as greater premorbid IQ deficit presents a higher probability of developing the mental illness (Khandaker et al., 2011). The prodromal period is characterized by a slow cognitive decline preceding psychotic symptoms onset by approximately a decade, with a probable continued deterioration as the illness progresses (Kahn & Keefe, 2013). Fundamental cognitive dimensions were shown to be affected, namely speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004). The latter category includes theory of mind, attribution styles, facial emotional recognition, and emotional regulation, all of which have been reported to be impaired in individuals with schizophrenia (Green, Horan & Lee, 2015). Their consequence on the

development and presentation of this disorder highlights the importance of cognitive and socioemotional deficits in this illness (Kahn & Keefe, 2013).

Multiple environmental risk factors for schizophrenia have been investigated, and early life events such as maternal infection, obstetric complications and childhood adversities, as well as late factors such as exposure to stressful events during adulthood, cannabis use, low serum folate levels (Belbasis et al., 2018), urban living, and migration (Murray et al., 2017), were shown to increase the risk for developing schizophrenia spectrum disorders (Matheson et al., 2011). Although environmental factors are important contributors to this phenotype, genetic factors account for a significant portion of the overall high heritability ($h^2$ = 0.79) with concordance rates over 0.33 in monozygotic twins (Hilker et al., 2018; Riley & Kendler, 2010). Some susceptibility genes have shown association with the disorder, but current understanding of schizophrenia relies on a multigenic model where several genes are involved in early brain maturation (Weinberger & Levitt, 2011) and are hypothesized to provide small contributions to the overall disease vulnerability (Zhang & Malhotra, 2013). Together, these findings suggest a neurodevelopmental model for schizophrenia where a predisposing genetic make-up interacts with the environment to disrupt normal neural development which promote the symptoms that are observed in the disease (Murray et al., 2017).

### 1.1.1 Neurobiology of schizophrenia

Current understanding of the pathophysiology of schizophrenia is founded in the dysregulation of at least three interrelated neurochemical networks (Stahl, 2018). The classic dopamine hypothesis of psychosis stipulates an abnormality primarily in the mesolimbic pathway (i.e., ventral tegmental area to ventral striatum) (Abi-Dargham & Grace, 2011). Positive symptoms observed in schizophrenia would be the consequence of increased presynaptic dopamine

synthesis and release (Howes et al., 2012) leading to a hyperdopaminergic state at $D_2$ receptors in the nucleus accumbens. Concurrent blunted dopaminergic activity at $D_1$ receptors in the mesocortical pathway (i.e., ventral tegmental area to prefrontal cortex) would explain the negative (ventromedial projections) and cognitive (dorsolateral projections) symptoms (Abi-Dargham & Grace, 2011; Stahl, 2013). Evidence from psychostimulant (e.g., amphetamine) challenge and positron emission tomography (PET) studies have corroborated striatal dopaminergic dysfunctions in schizophrenia (Kesby et al., 2018). These alterations were proposed to be associated with aberrant attribution of salience, a process thought to be central for the occurrence of positive symptoms (Winton-Brown et al., 2014). Altered salience processing and dopaminergic dysregulation in schizophrenia are hypothesized to mediate the impaired reward-related processing as well (Whitton, Treadway & Pizzagalli, 2015). The heterogenous response of psychotic symptoms to first-generation dopamine receptor blocking agents, however, suggests the implication of complementary networks in the pathophysiology of this disorder (Krystal & Moghaddam, 2011; Nickl-Jockschat & Abel, 2016). Hypoactive NMDA (i.e., glutamatergic) receptors on GABA interneurons in the prefrontal cortex have been posited to lead to an overactive cortico-brainstem glutamate pathway which projects to the ventral tegmental area (Schwartz, Sachdeva & Stahl, 2012). This would elicit both downstream dopaminergic mesocortical hyperactivity and mesolimbic hypoactivity (Stahl, 2013; Stahl, 2018). In keeping with glutamatergic processes, intoxication by dissociative anesthetics such as ketamine and phencyclidine, as well as the auto-immune disorder anti-NMDA encephalitis, reproduce cognitive and negative features of psychotic disorders in addition to hallucinations and delusions (Gründer & Cumming, 2016; Uno & Coyle, 2019). A growing number of magnetic resonance spectroscopy investigations have further provided support for glutamatergic

dysregulations in medial prefrontal regions (Marsman et al., 2013), basal ganglia, thalamus, and medial temporal lobe (Merritt et al., 2016). Overactivated mesolimbic dopaminergic pathways may equally result from hyperactive serotonergic receptors on glutamate neurons leading to the release of glutamate in the ventral tegmental area (Stahl, 2018). The serotonergic hypothesis is supported by the psychomimetic properties of psychedelic drugs as well as the mechanism of second-generation antipsychotics, the former being an agonist and the latter a partial antagonist of serotonin receptors (Stepnicki, Kondej & Kaczor, 2018). Other neurotransmitters have been implicated as well in the pathogenesis of schizophrenia, including the cholinergic (Tani et al., 2015) and endocannabinoid systems (Desfossés et al., 2010).

## 1.2 Aggression in schizophrenia

Although most individuals with schizophrenia (>80%, Swanson et al. (2006)) are not aggressive or violent (Silverstein et al., 2015), there is a significant association between schizophrenia/ psychosis and extreme hostile behaviors (Fazel et al., 2009; Witt, van Dorn & Fazel, 2013). Studies found a 2.1 to 4.6 times increase in risk of violent or aggressive behaviors in individuals with schizophrenia as compared to the general population after accounting for factors potentially contributing to a higher rate of violence (Brennan, Mednick & Hodgins, 2000; Fazel et al., 2009; Hodgins, 2008; Whiting et al., 2021). Individuals with schizophrenia are estimated to be responsible for 5% of violent crimes (Fazel & Grann, 2006) and over 6% of homicides (Hodgins & Janson, 2002). These numbers are very disproportionate, particularly when considering the low prevalence of the disorder (<1%, NIMH (2018)) and that only a subgroup of individuals with schizophrenia perpetrate the majority of the violence reported (Hodgins, 2008; Walsh et al., 2004). This minority represents an ongoing challenge for mental health service providers (Hodgins, Piatosa & Schiffer, 2013).

Aggressiveness is an early sign of psychotic relapse (Fond et al., 2019) and a predictor of physical assault (Sun et al., 2021). In addition to their direct effect, violent behaviors in schizophrenia lead to the stigmatization of mentally ill individuals, particularly those diagnosed with schizophrenia (Torrey, 2011). The victimization of individuals with schizophrenia is a consequence of violence within this population, which in turn increases the likelihood for violence (Buchanan et al., 2019; Witt et al., 2013). Aggressive behaviors interfere with treatment (Volavka & Citrome, 2008) and negatively impacts care, raising the burden of illness for both caregivers (i.e., treating team and families) (Brain et al., 2018) and society. In fact, a bed in a specialized forensic psychiatric hospital costs between $275,000 - $375,000/year (Fazel et al., 2016). For these reasons it is important to investigate the factors underlying the emergence of such behaviors in schizophrenia.

Aggression is defined as a spectrum ranging from hostile, threatening, to overt violence directed towards someone or something with the intention to inflict damage (Coccaro et al., 2011; Wise, Lyketsos & Onyike, 2019). Violent behaviors are thought of as an extreme form of aggression, as their goal is severe physical harm (Allen & Anderson, 2017). Male gender (Hachtel, Harries, et al., 2018; Witt, Lichtenstein & Fazel, 2015), symptomatology (e.g., higher positive symptoms, lack of insight, lower negative symptoms) (Bulgari et al., 2017; Hodgins & Riaz, 2011; Reinharth et al., 2014), treatment non-adherence (Buchanan et al., 2019; Witt et al., 2013), substance use (Fazel et al., 2009; Rund, 2018) and severity (Buchanan et al., 2019), as well as comorbid personality disorder (i.e., antisocial personality disorder, conduct disorder in childhood) (Hachtel, Harries, et al., 2018; Hodgins, 2017) are among the principal factors associated with violence in individuals with schizophrenia and psychosis. Cognitive impairments have not been consistently associated with violence in this patient population

(Bulgari et al., 2017; Rund, 2018) and a large meta-analysis failed to find a significant contribution of cognition to the risk of aggression in psychosis (Witt et al., 2013). Nevertheless, neurocognitive and social cognitive deficits (Darmedru, Demily & Franck, 2017; Lamsma et al., 2020) including global cognitive (Engelstad et al., 2018; Reinharth et al., 2014) and verbal learning impairments (Ahmed et al., 2018; Engelstad et al., 2018), as well as poor facial affect recognition (Bulgari et al., 2020; Sedgwick et al., 2017), were suggested by some studies to increase the propensity for aggressive behaviors in schizophrenia or other psychotic disorders (Rund, 2018). Poor impulse control (Witt et al., 2013) in conjunction with negative affectivity (i.e., anger, Reagu et al. (2013)) were proposed to be factors as well. Therefore, the relation between cognitive deficit and aggression among violent offenders with schizophrenia might be mediated by an impaired regulation of negative affect (Ahmed et al., 2018).

### 1.2.1 Trajectories

There is a considerable amount of heterogeneity in risk profiles and patterns of offending/aggression in schizophrenia and psychosis (Bo et al., 2011). In recent years, studies have highlighted factors and developmental pathways shared among individuals with and without psychosis leading to violent behavior, as well as some factors that are considered to be specific to schizophrenia and psychosis in the etiology of violence (Hodgins, 2008). This led to the currently prevalent two pathway conceptualization of violence in schizophrenia, a model that has garnered substantial corroboration (Kooyman & Walsh, 2011; Lamsma & Harte, 2015). Slight variations on this model have been considered, but most differentiate *i)* individuals with a history of violence and aggression in childhood preceding the onset of psychotic symptoms (i.e., early starters) from *ii)* those for whom violent behaviors present in adulthood, subsequent or concurrent to illness onset (i.e., late starters) (Bo et al., 2011; Hodgins, 2017).

The early starter group of violent persons with schizophrenia would display behaviors congruent with conduct disorder (CD) at an early age (prior to 15 years old), which would continue throughout their lifetime, including the onset and course of schizophrenia (Hodgins, 2008; Moffitt, 1993). CD is characterized by a persistent pattern of behaviors which includes the presence of at least 3 of the following 15 behaviors during a period of 12 months or more: aggression towards people and animals (i.e., bullying, physical fight, use of weapons, cruelty to people, cruelty to animals, mugging/extortion, forced sexual acts), destruction of property (i.e., fire setting or by other means), deceitfulness or theft (i.e., breaking and entering, con, shoplifting), and serious violations of rules (i.e., disobeying curfews, running away, truancy in school). Some might further display limited prosocial emotions (i.e., lack of remorse or guilt, callousness) (American Psychiatric Association, 2013b). In adulthood (>18 years old), these behaviors could progress to antisocial personality disorder (ASPD). ASPD is characterized by a disregard for the rights of others and includes 3 or more of the following: failure to conform to the law, deceitfulness, impulsivity, irritability and aggressiveness, disregard for the safety of others, irresponsibility, and lack of remorse (American Psychiatric Association, 2013a). As CD in the general population has been shown to be related to violence in adulthood (Blair, Leibenluft & Pine, 2014), conduct disorder and potentially ensuing ASPD would therefore be the primary explanation for the violent behaviors manifested by this subgroup of individuals with schizophrenia (Lamsma & Harte, 2015). Conversely, the aggression in the late starter group would be associated with the psychopathology of schizophrenia, namely symptoms of delusion and hallucination as well as other core features of the illness (Bo et al., 2011). Given these two distinct trajectories for the emergence of aggressive and violent behaviors in schizophrenia, the determinants are posited to be different as well (Hodgins et al., 2013).

### 1.2.2 Early starters

A certain amount of shared pathogenesis between CD and schizophrenia is implied by the early starter trajectory. Neurodevelopmental frameworks elaborated in both schizophrenia and CD have highlighted many risk factors common to the two psychopathologies (McDonough-Caplan & Beauchaine, 2018; Murray et al., 2017; Weinberger & Levitt, 2011). Hodgins (2017) noted that "genetic and environmental factors associated with schizophrenia promote CD", providing a potential explanation for their co-occurrence within the same individuals (Hodgins, 2008).

With recent studies proposing common genetic origins to multiple psychiatric disorders due to gene pleiotropy (i.e., one gene contributing to multiple phenotypes) (Pettersson, Larsson & Lichtenstein, 2016), an argument can be made for shared genetics underlying violent behaviors in individuals with CD/ASPD and schizophrenia. Given the implication of the dopaminergic and serotonergic networks in CD (McDonough-Caplan & Beauchaine, 2018), ASPD (Pemment, 2013), and schizophrenia (Stahl, 2018), associated candidate genes are likely to be involved. Polymorphisms of the *COMT* gene encoding for catecholamine (e.g., dopamine) degrading enzyme, the *5-HTTLPR* region encoding for serotonin transporter, and the *MAOA* gene encoding for monoamine (e.g., dopamine, serotonin, norepinephrine) degrading enzyme have received the most attention in the violence literature (Weeland et al., 2015). However, a transdiagnostic meta-analysis of these polymorphisms (Vassos, Collier & Fazel, 2014) and a small genome-wide association study in schizophrenia (Bani-Fatemi et al., 2020) failed to observe significant genetic associations with aggression.

Pre/peri-natal adversities are thought to be implicated in the pathogenesis of schizophrenia (Giannopoulou et al., 2018; Weinberger & Levitt, 2011) and conduct disorder (Buchmann et al., 2013; Provencal, Booij & Tremblay, 2015). Limited and non-replicated

reports (Cannon et al., 2002) have associated viral infection during gestation (Tehrani et al., 1998) and neonatal complications (Hodgins, Kratzer & McNeil, 2002) with violence in schizophrenia. These factors seem to have an anticipatory effect on illness onset rather than be pathology specific (Buoli et al., 2016). Similarly, early-life exposure to challenging psychosocial environments including mental illness, violence, and substance misuse are more frequently encountered in the life of individuals with poorer mental health (Hughes et al., 2016; Patel et al., 2016). Childhood adversities, especially victimization, were found to be associated with later manifestation of psychotic symptoms (childhood maltreatment, DeRosse et al. (2014)), conduct disorder (sexual abuse, Maniglio (2015)), and diagnosis of ASPD (physical abuse, Luntz and Widom (1994)). More specifically, the manifestation of violence in adulthood among individuals with schizophrenia spectrum disorders was linked with domestic violence (Oakley et al., 2016) and physical/sexual abuse (Buchanan et al., 2019; Witt et al., 2013) early in life. Therefore, a difficult environment during childhood could contribute to the joint development of the two disorders.

An overlapping etiology between CD and schizophrenia might explain the prevalence of over 40% of persons with schizophrenia spectrum disorders reporting behaviors congruent with conduct disorder in childhood (Kim-Cohen et al., 2003; Oakley et al., 2016) versus 12% in the general population (Nock et al., 2006) . These factors substantiate a neural diathesis-stress model, where biological predispositions interact with early life adversities to impact brain development and disrupt neurodevelopment (Birnbaum & Weinberger, 2017). This effect could be possibly mediated by the stress axis (Lovallo et al., 2017). The dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has received extensive attention in the neural diathesis-stress model of schizophrenia (Pruessner et al., 2017) and an emergent support in

CD/ASPD (Holz et al., 2018). Prolonged activation of the HPA axis due to stressful events might lead to the augmentation of dopamine synthesis, which has been linked to psychosis (Pruessner et al., 2017). Conversely, it could induce a chronically blunted HPA axis reactivity in CD/antisocial personality through an interaction with a disrupted serotonergic system (Armstrong et al., 2017; Ouellet-Morin et al., 2011). These alterations could predispose to violence by impairing emotional and cognitive functions in individuals with schizophrenia (Lamsma & Harte, 2015).

In fact, socioemotional deficits have been proposed to foster the emergence of violent behaviors (Roberton, Daffern & Bucks, 2012). The decreased ability to perceive, understand and manage emotions were associated with aggression in children, adolescent and adults (García-Sancho, Salguero & Fernández-Berrocal, 2014). The lack of concern for other's feelings (i.e., callousness) and difficulty to manage negative emotionality were posited to lead to aggressive behaviors in children with conduct disorder (Pardini & Frick, 2013). Maladaptive emotion regulation (Roberton, Daffern & Bucks, 2014) and negative emotion processing (i.e., anger) (Chereji, Pintea & David, 2012) were further reported in adult offenders. Beyond general deficits, impaired facial affect recognition was observed in individuals with CD (Hodgins et al., 2013), antisocial behaviors (Marsh & Blair, 2008), schizophrenia (Green et al., 2015), as well as comorbid ASPD/aggression and schizophrenia (Bulgari et al., 2020; Sedgwick et al., 2017). These results suggest impaired social-affective information processing in violent individuals to be a potential factor for adopting aggressive behaviors in individuals with schizophrenia presenting with those comorbidities (Hodgins et al., 2013; Sedgwick et al., 2017).

### 1.2.3 Late starters

Contrary to individuals with schizophrenia who have a history violence/CD in childhood preceding the onset of psychotic symptoms, violent behaviors in late starters are manifested following illness onset (Tengström, Hodgins & Kullgren, 2001). Given the late onset, brain changes associated with the first episode of psychosis were proposed to induce neural modifications increasing the probability to adopt these behaviors (Hodgins et al., 2013). This would imply an etiology tied to the pathogenesis of schizophrenia, even though violence is displayed only by a subgroup of individuals (Hodgins et al., 2013). As a result, violence could be linked to the presence of positive symptoms (Hachtel, Harries, et al., 2018; Hodgins & Riaz, 2011) and be mediated by a dysregulation of the dopaminergic system (Lamsma & Harte, 2015). This is supported by the increased risk for violence in treatment nonadherent patients (Buchanan et al., 2019) and the higher rate of homicide in first episode of psychosis preceding initial treatment (Nielssen & Large, 2010).

However, meta-analyses (Fazel et al., 2009; Witt et al., 2013) as well as large cohort (Buchanan et al., 2019) and cross-sectional (Sun et al., 2021) studies have inconsistently associated psychotic symptoms with violence in schizophrenia/psychosis. This is reflected by risk assessment tools for violent behaviors and recidivism, as some consider positive symptoms and psychotic disorders as predictors (e.g., Historical Clinical Risk Management-20 (HCR-20), Douglas et al. (2013)) while others disregard them (e.g., Violence Risk Appraisal Guide - Revised (VRAG), Harris et al. (2015)). Alternatively, features related to positive symptomatology, such as the negative affect associated with paranoid ideation (Coid et al., 2016), the anger associated with delusions (Ullrich, Keers & Coid, 2014), or the patients' powerlessness towards their hallucinations (Berman, Duffy & Serper, 2010) might explain the

relation with violent behaviors. Therefore, dysregulated emotions in relation to psychotic symptoms would be the driving factor for aggression in this subgroup, not the presence of psychosis alone (Adams & Yanos, 2020).

Based on the currently available evidence, the two-pathway conceptualization differentiating trajectories of aggression in schizophrenia with regards to the onset of the behaviors (i.e., early vs. late starter) appears to be reasonably congruent with the neurodevelopmental model of both CD and schizophrenia. Furthermore, the factors identified by these trajectories explain a non-negligible fraction of the violence and offending observed in individuals with schizophrenia. Risk assessment tools, either actuarial (e.g., VRAG) or structured professional judgement (e.g., HCR-20), rely at their core on a combination of features associated with conduct disorder/ASPD (e.g., aggressive/violent behavior at a young age) and major psychiatric illness (e.g., adherence to therapy) to predict the risk of future violence (Shapiro & Noe, 2015; Singh, Serper, et al., 2011). Investigations in early and late starters also highlight the need to improve our understanding of the mechanisms underlying impaired cognitive functions, including emotion processing/regulation, in the co-occurrence of aggression and schizophrenia.

## 1.3 Treatment of aggression

### 1.3.1 Pharmacotherapy

The National Institute for Health and Care Excellence (2013) and American Psychiatric Association (2020) recommend the use of antipsychotics as a first-line pharmacological treatment for individuals with schizophrenia. Little to no clinically significant differences in efficacy have been reported between most oral antipsychotics for the initial treatment, acute

treatment, and relapse prevention (National Institute for Health and Care Excellence, 2013), with the possible exception of clozapine (American Psychiatric Association, 2020). Antipsychotics share a mechanism of action in decreasing positive symptoms, as their effect is currently understood to be mediated by striatal $D_2$ dopamine receptor blockade (Lally & MacCabe, 2015).

The benefit of antipsychotics on aggressive behavior has been reported by many studies (Comai, Tau, Pavlovic, et al., 2012). A recent meta-analysis determined atypical antipsychotics, specifically clozapine, to have a significant but small effect in decreasing aggressive/hostile behaviors in individuals with schizophrenia spectrum disorders (Faay, Czobor & Sommer, 2018). The implication of the serotoninergic system in the neurobiology of human aggression (Duke et al., 2013) could explain the efficacy of atypical antipsychotics as they tend to be more potent serotonin antagonists than typical antipsychotics (Stahl, 2013). The American Psychiatric Association (2020) recommends clozapine for individuals with schizophrenia presenting an increased risk for aggression despite other treatments and is not indicated for acute aggression management (Quinn & Kolla, 2017). Limited evidence also supports clozapine to have a beneficial impact on risk factors for aggression in this population (Strassnig et al., 2020) such as substance use (Krause et al., 2019) and recurrent suicidal behaviors (American Psychiatric Association, 2020; Novartis, 2002). There is also preliminary evidence for violence reduction with clozapine in individuals with comorbid CD in schizophrenia (Krakowski, Tural & Czobor, 2021) and in individuals with antisocial behaviors (Andreea et al., 2021) or personality disorder (pilot study, see Brown et al. (2014)). Furthermore, clozapine was associated with self-reported improvement in quality of life and social abilities in forensic patients (Qurashi et al., 2015).

Beyond antipsychotics, limited evidence supports the efficacy of anticonvulsants such as valproate (Tseng et al., 2016) and carbamazepine (Leucht et al., 2014) in decreasing aggression in schizophrenia despite their use in clinical practice. Medication adherence is another consideration, as it is one of the few modifiable risk factors for aggressive behaviors in schizophrenia (Strassnig et al., 2020). Long acting injectable antipsychotics are recommended to improve treatment adherence (American Psychiatric Association, 2020). However, there is little research to date supporting aggression reduction with depot medication in schizophrenia (Mohr et al., 2017).

### 1.3.2 Psychotherapy

Psychotherapeutic interventions utilized in general psychiatry with evidence for violence reduction in schizophrenia either aim for psychotic symptom reduction or functional impairment management (Dumont et al., 2018; Quinn & Kolla, 2017; Simpson & Penney, 2011). Cognitive Behavioral Therapy (CBT) focuses on maladaptive cognitions by addressing biases to alleviate emotional distress and reduce problematic behaviors (Hofmann et al., 2012). CBT was shown to have a small (Jauhar et al., 2014) to moderate effect (National Collaborating Centre for Mental Health, 2014) in reducing overall symptom severity in persons with schizophrenia or psychosis in comparison to standard care. CBT was found to have little to no effect on negative symptoms when examined separately (Velthorst et al., 2015). In offenders with mental health issues, the intervention was tentatively reported by systematic reviews to ameliorate problem solving, anger management, self-harm (Duncan et al., 2006), as well as reduce overall aggression (Ross et al., 2013) and aggression in psychosis (Rampling et al., 2016) based on a limited number of low-evidence-level studies. Despite the lack of high-quality studies, symptom

management with CBT was suggested to improve aggression in individuals with schizophrenia (Dumont et al., 2018; Quinn & Kolla, 2017).

Cognitive Remediation Therapy (CRT) addresses cognitive problems at the basis of functional impairments. Recent meta-analyses have concluded that CRT provides a small to moderate improvement in cognitive dysfunctions and psychosocial functioning in individuals with early (Revell et al., 2015) and chronic schizophrenia spectrum disorders (Cella et al., 2020; Norman et al., 2017; Vita et al., 2021; Wykes et al., 2011). CRT was shown to reduce negative symptoms as well (Cella et al., 2017). Ahmed et al. (2015) reported significant improvements in negative symptoms and executive functions together with a decrease in aggression in the sole study investigating cognitive remediation in forensic patients with schizophrenia spectrum disorders. Improvements in social functioning, including a reduction of disturbing and aggressive behaviors, were reported in non-forensic inpatients with schizophrenia following facial affect recognition training (Byrne et al., 2015). Similarly, Integrated Psychological Therapy and Reasoning and Rehabilitation programs were found to be effective in improving prosocial behaviors in individuals with schizophrenia (Roder et al., 2006; Roder, Mueller & Schmidt, 2011) and non-psychiatric offenders (Berman, 2004) respectively. There are currently few to no studies assessing the efficacy of the latter interventions in forensic patients with schizophrenia despite being already implemented clinically (Dumont et al., 2020; Müller-Isberner, 2017; Quinn & Kolla, 2017). Overall, cognitive and social skills could potentially be therapeutic targets in violent individuals with schizophrenia (Darmedru et al., 2017; Jones & Harvey, 2020).

Alternatively, Measurement Based Care (MBC) tools such as the HCR-20 (Douglas et al., 2013) and the DUNDRUM toolkit (Kennedy et al., 2010) were developed for forensic

psychiatric patients to tailor the treatment to the individual (Glancy et al., 2021; Lecomte & Leclerc, 2012). The former has been employed in research to predict violence (Cote et al., 2012). Two studies have reported lower reconviction rates in samples of forensic patients with high prevalence of schizophrenia (>79%) following the clinical implementation of the HCR-20 (Pedersen, Ramussen & Elsass, 2012; Vojt, Thomson & Marshall, 2013), indicating that individualized risk assessment in MBC could inform ongoing patient management to reduce the occurrence of such behaviors (Cho et al., 2019; Pedersen et al., 2012).

In summary, cognitive-behavioral and pharmacological (i.e., clozapine) interventions targeting psychotic symptoms garner the most evidence currently for the management of aggressive behaviors in schizophrenia (Dumont et al., 2018; Faay et al., 2018; Quinn & Kolla, 2017). Additionally, the potential efficacy of therapies aimed at improving cognitive and psychosocial dysfunctions supports the contribution of these functional impairments to aggression and violence in this patient population (Darmedru et al., 2017).

## 1.4 Neuroimaging in schizophrenia

### 1.4.1 Structural neuroimaging

Despite the incomplete knowledge of the underlying neurochemistry, neuroanatomical models relying on non-invasive imaging techniques have allowed to investigate brain alterations involved in schizophrenia (Kesby et al., 2018). Given the significant breadth and heterogeneity of the neuroimaging literature pertaining to this psychopathology, meta-analyses have been able to extract general patterns of variations (Bzdok & Eickhoff, 2016). Structural magnetic resonance imaging (MRI) studies have demonstrated global brain atrophy, widespread cortical thinning, and ventricular enlargement in individuals with schizophrenia when compared to

healthy controls (Shepherd et al., 2012; van Erp et al., 2018; Wright et al., 2000). Reductions in gray matter volume with small to moderate effect size were predominantly observed in fronto-temporo-limbic regions including *i)* the superior, middle, and inferior frontal gyri, as well as prefrontal (PFC) and orbitofrontal cortex (OFC); *ii)* the fusiform gyrus and insular cortex; and *iii)* the cingular (anterior and posterior) cortex, parahippocampal gyrus, hippocampus, amygdala, nucleus accumbens, and thalamus (Glahn et al., 2008; Haijma et al., 2012). Conversely, preserved putamen and caudate volumes were reported in medicated patients, likely due to the effect of antipsychotics (Haijma et al., 2012; van Erp et al., 2016). Patterns of cortical thickness alteration were similar to the volume deficits, with reduced orbitofrontal-insular-temporal thickness (van Erp et al., 2018). Volume reduction was also observed in parietal and occipital lobes, as well as in the cerebellum (Haijma et al., 2012), whereas precentral, parietal, and precuneus cortical thickness was increased in individuals with schizophrenia (van Erp et al., 2018). Further structural analyses demonstrated global dysconnectivity in this disorder, with white matter volume reduction and abnormal diffusion measured by fractional anisotropy across most major fasciculi, particularly the frontotemporal, interhemispheric, and corticothalamic tracts (Kelly et al., 2018; Vitolo et al., 2017).

Recent efforts by the ENIGMA consortium (Bearden & Thompson, 2017) pooling large sample sizes have helped in clarifying the previously ambiguous associations between structural variations and cognition/symptoms in schizophrenia. Structural brain deficits were associated with overall worse cognition and impaired working memory and visual learning (Kochunov et al., 2020). Negative symptoms severity was associated with overall brain and white matter deficits (Kochunov et al., 2020) and medial OFC thinning (Walton et al., 2018). Increased positive symptoms severity was associated with cortical thinning in the superior temporal gyrus

(Walton et al., 2017), inferior-middle temporal gyrus, medial orbitofrontal gyrus, and anterior cingulate cortex (ACC) (Wong et al., 2020). Hostility/poor impulse control was associated with ACC, temporal and insular cortex thinning (Wong et al., 2020). Other meta-analyses have shown the volumetric brain patterns to be present to a lesser extent in antipsychotic-naïve patients (Haijma et al., 2012) and progress with illness duration (Fusar-Poli et al., 2013). Cortical thickness and subcortical volume deficits were already developed around illness onset and remained stable, as opposed to white matter deficits which progressed with chronicity (Kochunov et al., 2020). These features are generally in line with the neurodevelopmental model of schizophrenia and indicate an additional component of disease progression throughout the course of the illness (Bzdok & Eickhoff, 2016; Kochunov et al., 2020; Olabi et al., 2011).

### 1.4.2 Functional neuroimaging

Resting-state functional MRI (fMRI) studies investigating the intrinsic interactions between brain regions showed widespread dysconnectivity within and between functional networks in individuals with schizophrenia when compared to healthy controls (Dong, Wang, Chang, et al., 2018; Li et al., 2019). Commonly recognized large-scale functional neurocognitive networks include the occipital, pericentral, dorsal frontal parietal, lateral frontoparietal, midcingulo-insular, and frontoparietal networks underlying the visual, somatomotor, attentional, cognitive control, salience, and default cognitive domains respectively (Uddin, Yeo & Spreng, 2019). Higher cognitive functions are understood to be served by the default-mode (i.e., self-referential mental processes), central executive/ frontoparietal (i.e., goal directed information control), and salience (i.e., identification of relevant information) networks (Menon, 2011; Uddin et al., 2019). Reduced connectivity in these latter networks in schizophrenia support the triple network model (Dong, Wang, Chang, et al., 2018; Li et al., 2019) which postulates that dysfunctions in

those three core neurocognitive networks are common to many psychopathologies (Menon, 2011). Certain alterations remain characteristic of schizophrenia, as dysconnectivity in the insula, striatum and thalamus were reported to be disorder-specific (Brandl et al., 2019). Default-mode network connectivity was observed to be disrupted at early stages of the disorder and aberrant connectivity seemed to extend through the brain with illness progression (Gong et al., 2020). The disruption of functional networks could result from the subjacent altered cerebral structures (Vitolo et al., 2017).

In contrast to structural imaging and resting-state connectivity, task-based fMRI examines neural dysfunctions in particular cognitive states (Meyer-Lindenberg & Bullmore, 2010). Crossley et al. (2016) undertook to summarize the inconsistent functional neuroimaging literature in schizophrenia and found grossly localized task-specific alterations when comparing individuals with schizophrenia to healthy controls. The broad characterization of the deficits includes underactive prefrontal regions and overactive medial temporal and anterior cingular cortex in working memory tasks. Similar deficits were observed (i.e., underactive DLPFC) in unaffected relatives of individuals with schizophrenia (Zhang, Picchioni, et al., 2016) and had a higher probability of occurring in individuals with psychotic disorders when compared to other psychopathologies (McTeague et al., 2017), making this one of the more reliable neurofunctional markers of the disease. Underactive hippocampus in addition to overactive medial temporal regions were also reported in episodic memory tasks (Crossley et al., 2016). Underactive anterior and middle cingulate cortex were associated with both attentional and inhibitory tasks, with overactive supramarginal gyrus during the former and overactive parietal and occipital cortex during the latter (Crossley et al., 2016). In accordance with these results, a previous meta-analysis of executive task processing in individuals with schizophrenia by

Minzenberg et al. (2009) highlighted diffuse under-recruitment of prefrontal cortices (DLPFC, VLPFC), ACC, subcortical regions (thalamus, putamen), and temporo-parietal cortex. Notably, the pattern of regions activated by the tasks in patients was similar to the distribution of regions activated in healthy controls (Minzenberg et al., 2009). The relative dysregulation in schizophrenia of regions involved in top-down control (i.e., DLPFC) and performance monitoring (i.e., ACC) could therefore indicate an impaired recruitment of the cognitive control network when executive functions are being solicited (Penadés et al., 2019). Overall, these results offer potential neural mechanisms associated with the substantial deficit in executive functioning reported in this patient population.

Neural processes associated with social cognition are equally impaired in schizophrenia (Crossley et al., 2016). Studies have reported blunted amygdalar response in schizophrenia to facial (Li et al., 2010; Taylor et al., 2012) and aversive emotional stimuli (Anticevic et al., 2012). A more extensive blunted limbic response during threatening face perception, including the amygdala, hippocampus, and putamen, was further coupled with MPFC overactivation (Dong, Wang, Jia, et al., 2018). In contrast, Dugré et al. (2019) observed overactive amygdala, putamen, hippocampus, and insula in individuals with schizophrenia in a meta-analysis of neutral stimuli processing. An increased reactivity of the limbic system during the processing of non-threatening information, consistent with the aberrant salience hypothesis of psychosis, is a probable explanation for the between-study discrepancies (Anticevic et al., 2012; Dugré et al., 2019). Underactive DLPFC and VLPFC during emotion recognition (Jani & Kasparek, 2018) and ACC during emotion perception (Taylor et al., 2012) were reported as well.

During theory of mind tasks, underactive medial prefrontal and lateral temporal cortex, as well as pallidum, and overactive frontal regions and supramarginal cortex were observed

(Crossley et al., 2016). Dysfunctions in VLPFC during empathy and the posterior temporo-parietal junction during intention attribution were also reported (Vucurovic, Caillies & Kaladjian, 2020). The general disruption in the social brain network has been attributed to a diminished difference between the neural representation of mentalizing and non-mentalizing processes in schizophrenia (Kronbichler et al., 2017). This could potentially underlie the impaired self-other distinction (Jani & Kasparek, 2018) and reasoning in social context (Vucurovic et al., 2020) seen clinically in this patient population.

Beyond examining the association between distinct brain regions, a systems approach has been increasingly favored for investigating neural activity of emotional processing as integrated functional networks (Pessoa, 2017). In a large multi-site data-driven study, Karrer et al. (2019) found the intrinsic fMRI connectivity of regions implicated in social-affective functions to be of higher discriminative value than those associated with traditionally investigated cognitive domains (e.g., working-memory) to differentiate individuals with schizophrenia from healthy controls. This was especially the case for brain networks derived from task-based neuroimaging studies employing categories of socially relevant stimuli (e.g., faces) and negative emotions (e.g., sadness, fear). Taken together, these results reflect the importance of impaired social-emotional processing in this psychopathology.

Similarly to social-affective cue misinterpretation, reward processing is impaired in schizophrenia (Meyer-Lindenberg & Bullmore, 2010). A blunted ventral striatal activity during reward processing (Radua et al., 2015; Winton-Brown et al., 2014; Zhang, Lin, et al., 2016), anticipation (Leroy et al., 2020) and learning (Chase et al., 2018) has been consistently reported in the literature. Negative (Radua et al., 2015; Zhang, Lin, et al., 2016) more so than positive symptoms (Leroy et al., 2020) were associated with the hypoactivation. The relationship

between symptomatology and neural deficit might explain the impaired motivating and reinforcing effect of rewarding stimuli in schizophrenia (Radua et al., 2015). Reward anticipation was further associated with underactive cingulate/paracingulate gyri (Leroy et al., 2020), ACC, MPFC and caudate head (Zhang, Lin, et al., 2016).

## 1.5 Neuroimaging of aggression in schizophrenia

### 1.5.1 Neuroanatomy and neurochemistry of aggression

Evidence supports overarching factors to predispose a subgroup of individuals with schizophrenia to crime or violence (Hodgins, 2017). In both general and psychiatric populations, aggressive behaviors have been traditionally distinguished by their motivation (Allen & Anderson, 2017; Anderson & Kiehl, 2013). The predominant model employed in the neuroimaging literature broadly differentiates reactive from proactive violence/aggression, the former characterized as impulsive and associated with anger versus the latter being instrumental and predatory (Barratt et al., 1999; Poldrack et al., 2017; Rosell & Siever, 2015; Wise et al., 2019). Motivation-based domains of violence have been shown to be independent of personality disorder, as individuals with conduct disorder/ antisocial personality disorder can present both reactive and proactive aggressive behaviors (Anderson & Kiehl, 2013; Blair et al., 2014; McKinley, Patrick & Verona, 2018). Psychotic violence, associated with the symptomatology of schizophrenia and psychosis, was suggested to be a separate third sub-domain of violence (Stahl, 2014). As previously discussed, investigations found negative emotions elicited by positive psychotic symptoms to be important mediators in adopting violent behaviors (Adams & Yanos, 2020; Ullrich et al., 2014; Ullrich et al., 2018). Therefore, violence that is reactive or

psychotic would share common deficits in mechanisms such as emotion regulation/processing as well as inhibitory control (see Figure 1), and in corresponding neural circuits (Stahl, 2014).

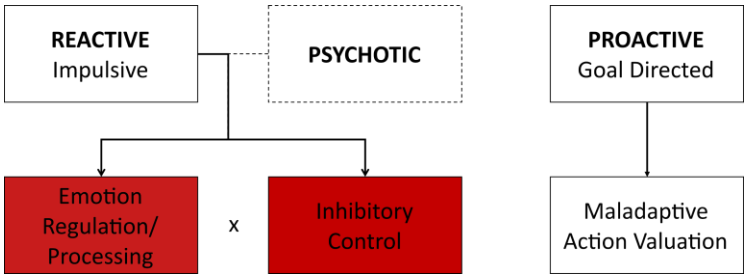


Figure 1. Motivation-based categorization of aggressive behaviors

The reactive and psychotic violence, subsequently referred to together as impulsive violence, are postulated to map onto neural systems that imply primarily cortico-limbic dysfunctions (Coccaro et al., 2011). Coccaro et al. (2011) suggested a neuroanatomical model recently updated for schizophrenia by Leclerc et al. (2018) where abnormal functioning of regions implicated in the *i)* generation of aggressive impulses, *ii)* emotion regulation and impulse control, as well as *iii)* decision making (i.e., impaired cost-benefit processing, Blair (2016)) and information processing would be associated with violent behaviors (see Figure 2). A faulty functioning or interaction of the aforementioned neural circuits would lead to a failure of regulating negative emotions and increase the propensity towards impulsive aggression and violence (Davidson, Putnam & Larson, 2000).

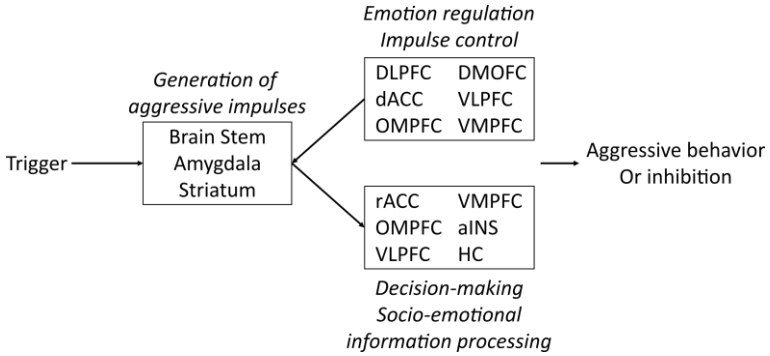


Figure 2. Neural circuits involved in impulsive aggressive behavior adapted from Leclerc et al. (2018) (License: 4635800712132)

Preliminary data based on animal and human lesion/stimulation studies have shown the periaqueductal gray area, located in the brainstem, and hypothalamus to be associated with aggressive responding (Feltes & de Boer, 2021; Haller, 2020). An overactive limbic system mediating an excessive reactivity or sensitivity to negative/threatening stimuli has been more robustly demonstrated in impulsive violence (Bertsch, Florange & Herpertz, 2020; Stahl, 2014). Structural deficits and functional dysregulation of the amygdala were particularly associated with aggression (Coccaro et al., 2011; Davidson et al., 2000), although the relation appears to be less direct than originally hypothesized (Dugré et al., 2020; Fanning et al., 2017; Rosell & Siever, 2015). Aggressive behaviors, particularly predatory/instrumental (Stahl, 2014), were also associated with positive affect (e.g., pleasure) (Chester, 2017), lack of achieving a reward/goal (e.g., frustration) (Bertsch et al., 2020), and disrupted reward valuation (Blair, 2016). These processes are proposed to be facilitated by the striatum (Rosell & Siever, 2015) and to exert a reinforcing effect on aggressive behaviors (Fanning et al., 2017). The reward system was not originally considered in Coccaro et al. (2011)'s framework and has since been included in reactive violence models (Bertsch et al., 2020; Chester, 2017; Fanning et al., 2017; Leclerc et al., 2018), as an inability to learn from negative stimuli (i.e., punishment, Xu, Farver and Zhang (2009)) would be a process mediated by the striatum as well (Fanning et al., 2017).

Aggressive impulses originating from subcortical regions were suggested to be modulated by top-down executive processes, such as emotion regulation and inhibitory control (Bertsch et al., 2020), supported by a broad frontoparietal network (Puiu et al., 2020). The dorsolateral and ventral prefrontal cortices were shown to attenuate negative emotional responses (Coccaro et al., 2011; Fanning et al., 2017), and aggression was associated with aberrant recruitment or deficit of regions within this network (Haller, 2020; Wong et al., 2019;

Yang & Raine, 2009). Regulatory dysfunctions in aggression would further involve faulty socioemotional information processing, which relies on a general cortico-limbic-insular network (Bertsch et al., 2020; Coccaro et al., 2011). Processing of negative stimuli, such as anger, was shown to recruit the ACC and the anterior insula (Puiu et al., 2020). Therefore, a dysfunction in these networks would lead to a deficit in behavioral and emotional control, likely increasing the vulnerability to adopt aggressive behaviors (Bertsch et al., 2020). Conversely, context appropriate decision-making was associated with orbitofrontal and ventromedial prefrontal cortices (Bertsch et al., 2020; Blair, 2016). A dysfunction within these regions would lead to impaired decisions due to poorly motivated choices, which can result in risk-taking/impulsive behaviors including aggression (Blair, 2016).

The current understanding of the neurochemical basis of violence and aggression remains limited (Manchia et al., 2020). Multiple neurotransmitter systems have been considered including serotonin, dopamine, norepinephrine, glutamate, GABA, and vasopressin, as well as other neuropeptides (Pompili et al., 2017). The relationship between serotonin and aggression has been the most investigated (Manchia et al., 2017), where this neurotransmitter system is posited to be implicated in the inhibitory control (Davidson et al., 2000) over the impulsive aspects of aggressive behaviors (Coccaro et al., 2011; Comai, Tau & Gobbi, 2012). Accordingly, Duke et al. (2013) observed a small relationship between multi-method assessments of serotonin deficiency and increased aggression/hostility/anger in a transdiagnostic meta-analysis which included 3 studies of individuals with schizophrenia. The few published studies employing PET imaging with targeted probes in small samples of ASPD subjects further suggest regional dysfunctions of the serotonergic system (i.e., receptor or transporter function) in the DLPFC and brainstem, as well as potentially the ACC (Kolla & Houle, 2019). Lower *MAOA* (dopamine and

serotonin degrading enzyme) density was also observed in the OFC and ventral striatum of individuals with ASPD (Kolla & Bortolato, 2020; Kolla et al., 2015). Although less studied in the context of violence (Rosell & Siever, 2015), the dopaminergic system was proposed to be related to the motivational elements of antisocial behaviors (Comai, Tau & Gobbi, 2012). The scant literature in non-clinical healthy subjects is, however, contradictory (Rosell & Siever, 2015). Aggressivity was associated with decreased dopaminergic synthesis in the midbrain and the striatum (Schlüter et al., 2013), whereas increased dopamine release in the striatum was associated impulsive antisocial traits (Buckholtz et al., 2010). At present, the association between dopamine and aggressive behaviors is primarily derived from the psychopharmacological management of violence with antipsychotics in individuals with schizophrenia (Comai, Tau & Gobbi, 2012; Manchia et al., 2020).

### 1.5.2 Structural neuroimaging

To date, most neuroimaging investigations of violent individuals with schizophrenia (SCZ+V) have employed structural MRI. Reduced whole brain volume (Barkataki et al., 2006; Kumari et al., 2013; Schiffer et al., 2013), reduced volume in the hippocampus (Barkataki et al., 2006), parahippocampus (Yang, Raine, et al., 2010), thalamus (Kumari et al., 2013), anterior cingulate cortex (Kumari et al., 2014), cerebellum (Puri et al., 2008), right inferior temporal area and the right insular area (Kuroki et al., 2017), as well as increased volume in the putamen (Barkataki et al., 2006) have been reported in SCZ+V individuals. Furthermore, reduced cortical thickness in sensory motor regions (Narayan et al., 2007), precentral, parietal, temporal, and fusiform cortex, as well as increased cortical folding in visual and orbitofrontal cortex were observed in SCZ+V (Storvestre et al., 2019). Increased gray matter volumes were also found in the

hypothalamus, left putamen, right precuneus, and right inferior parietal cortex in men with schizophrenia and a history of conduct disorder (Schiffer et al., 2013).

Correlational studies have found higher levels of aggressive behaviors to be associated with larger orbitofrontal cortex (Hoptman et al., 2005) and caudate volumes (Hoptman et al., 2006), as well as reduced inferior frontal gyrus volumes (Schoretsanitis et al., 2019) in men with schizophrenia. Higher negative urgency correlated with reduced cortical thickness in orbitofrontal cortex and frontal pole (Hoptman et al., 2014), and high impulsivity correlated with reduced orbitofrontal and hippocampal volume (Kumari, Barkataki, et al., 2009) in aggressive individuals with schizophrenia. Finally, some found no deficits specific to SCZ+V individuals (Del Bene et al., 2016).

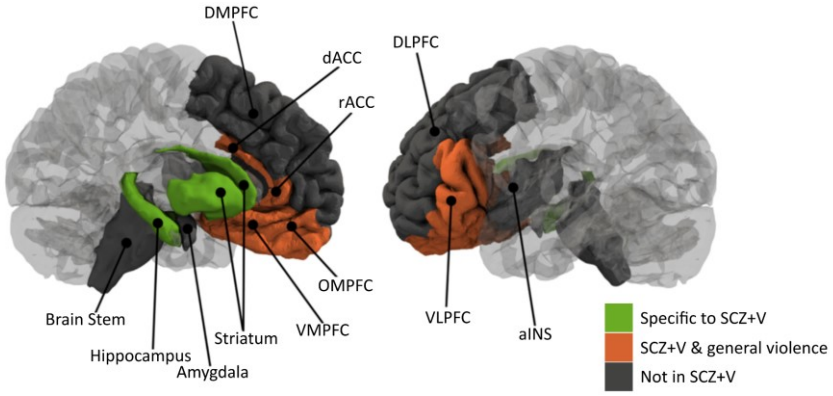


Figure 3. Structural correlates of aggression in psychosis adapted from Leclerc et al. (2018) (License: 4635800482639)

To a certain extent, structural neuroimaging results are concordant with Coccaro et al. (2011)'s cortico-limbic neuroanatomical model of impulsive aggression, albeit certain key regions were not shown to be impaired in SCZ+V (see Figure 3) (Leclerc et al., 2018). Regions implicated in socio-emotional processing (i.e., orbitofrontal cortex, ACC) seem more disrupted than inhibitory/regulatory regions (i.e., frontoparietal network) (Fjellvang, Grøning & Haukvik, 2018). Notably, only few studies reported amygdalar involvement (Barkataki et al., 2006; Tesli

et al., 2020) with results that did not differentiate violent men with schizophrenia (Leclerc et al., 2018). Conversely, the striatum and hippocampus were altered specifically in SCZ+V (see Figure 3). Larger striatal volumes might be the consequence of higher doses of antipsychotic medication (Ho et al., 2011) utilized in forensic patients (Margetić et al., 2017). It could also represent a corollary of dysfunctional reward-reinforcing system in individuals with schizophrenia prone to aggression (Leclerc et al., 2018). Reduced hippocampal volume might indicate a broader implication of the limbic system underlying violent behavior in schizophrenia, as it is a structure involved in threat learning (Montagrin, Saiote & Schiller, 2018). These two regions were added to Leclerc et al. (2018)'s updated neuroanatomical model of impulsive violence in schizophrenia (see Figure 2). Overall, structural findings were limited by between-articles inconsistencies (Fjellvang et al., 2018; Widmayer, Sowislo, et al., 2018). The only significant quantitative result evidenced by a meta-analysis based on 5 out of 16 studies is a decrease in total brain volume in violent individuals with schizophrenia, as compared to non-violent individuals with schizophrenia and healthy subjects (Widmayer, Sowislo, et al., 2018). This is an indication that the central nervous system might be affected in individuals with schizophrenia displaying aggressive and violent behaviors, without providing robust region-specific information or an insight into the processing of stimuli that may trigger violent behavior.

### 1.5.3 Connectivity

The few studies in SCZ+V individuals employing structural or functional connectivity tentatively suggest a cortico-limbic dysconnectivity (Coccaro et al., 2011). Lower white matter integrity was associated within the ventral prefrontal cortex with higher levels of aggression (Hoptman et al., 2002), and within inferior frontal regions with higher levels of impulsivity

(Hoptman et al., 2004) in individuals with schizophrenia. However, Tesli et al. (2019) observed no specific correlates of white matter integrity deficit with trait or state measures of violence and aggression in a large sample of individuals with schizophrenia. Studies using resting-state functional connectivity in individuals with schizophrenia reported reduced connectivity between the ventral prefrontal regions and amygdala, which correlated inversely with aggression (Hoptman et al., 2009), and between the ventral prefrontal regions and anterior cingulate cortex, which correlated inversely with urgency (Hoptman et al., 2014). Although aligned with current models of impulsive violence (Stahl, 2014), studies in structural and functional connectivity do not model discrete cognitive or emotional states associated with violent behavior, unlike investigations employing task-based functional imaging.

### 1.5.4 Functional neuroimaging

Currently, 7 published articles employed functional imaging to study violence in schizophrenia, excluding articles from our laboratory. Only 5 reported differences between violent and non-violent individuals with schizophrenia (see Figure 4) (Fjellvang et al., 2018; Widmayer, Borgwardt, et al., 2018). During a Go-NoGo task, Joyal et al. (2007) observed an increased activation in the primary somatosensory area, inferior parietal cortex and cerebellum, and a decreased activation in the precuneus and superior temporal gyrus in individuals with schizophrenia with comorbid antisocial personality disorder and substance use disorder as compared to non-violent individuals with schizophrenia. Conversely, Barkataki et al. (2008) found no differences during a Go-NoGo task between violent and non-violent individuals with schizophrenia. During a shock anticipation task, Kumari, Das, et al. (2009) reported an increased activity bilaterally in the medial prefrontal/cingulate gyrus and middle temporal gyrus, as well as in the right posterior cingulate/cuneus and left middle occipital gyrus. Kumari et al. (2006)

found a decreased activation in the right inferior parietal lobe in violent compared to non-violent individuals with schizophrenia in an n-back task. Finally, Schiffer et al. (2017) reported an increased activation in bilateral precuneus, left superior temporal sulcus, right fusiform areas, left VLPFC, and right DLPFC during a theory of mind task in violent individuals with schizophrenia and a history of conduct disorder compared to non-violent individuals with schizophrenia. The results vary substantially across studies due to the diverse paradigms implemented targeting inhibitory control, working memory, fear anticipation, and theory of mind.

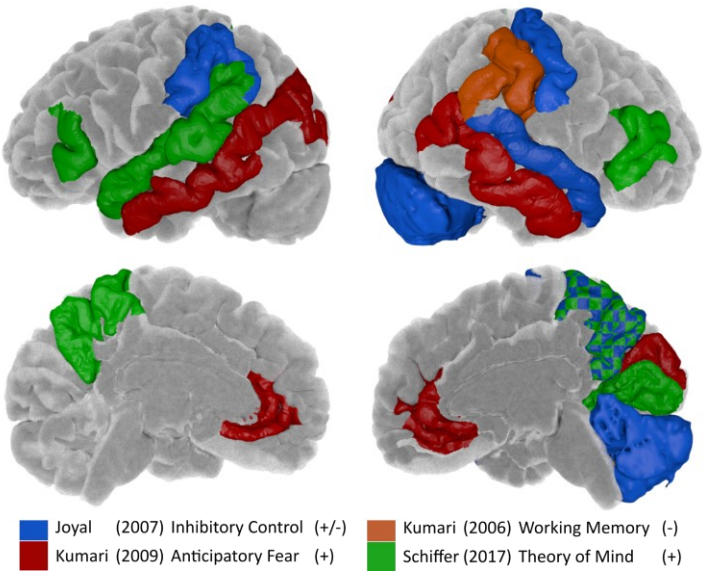


Figure 4. Functional correlates of aggression in psychosis (SCZ+V vs SCZ-V)

The remaining 2 functional studies used tasks related to emotion processing, although they lacked appropriate comparison groups. García-Martí et al. (2013) observed increased activation associated with higher aggressivity levels during an auditory emotional stimulation task in the left hippocampus and the right medial frontal gyrus in individuals with schizophrenia and a history of violence. Dolan and Fullam (2009) used a task based on implicit processing of fearful faces and observed a decrease in amygdalar activity associated with higher psychopathy

scores in individuals with schizophrenia. These results suggest functional abnormalities in brain regions involved in emotion regulation among individuals with SCZ+V during the processing of emotional cues.

The results from the extant literature in both structural and functional neuroimaging are difficult to interpret given the technical and theoretical limitations. Most studies are characterized by their heterogenous definition of aggression/violence, small sample sizes, lack of appropriate control groups, and use of region-of-interest approach over whole brain analysis (Cho et al., 2019). Furthermore, functional neuroimaging studies fail to model cognitive or emotional states related to the emergence of impulsive violence. Altered emotional processing/regulation (Green et al., 2015; Nuechterlein et al., 2004) and cognitive control with corresponding neural deficits (Crossley et al., 2016; Minzenberg et al., 2009) were found in individuals with schizophrenia. Dysregulated emotion processing and inhibitory control were suggested as potential mechanisms for aggressive behaviors (Bertsch et al., 2020; Coccaro et al., 2011; Davidson et al., 2000), particularly in this patient population (Adams & Yanos, 2020; Hodgins & Klein, 2017). Yet, only 2 studies have investigated emotional processing in relation to aggressive behaviors in schizophrenia, which presented with most of the above listed technical limitations (Dolan & Fullam, 2009; García-Martí et al., 2013). Furthermore, 2 studies investigated inhibitory control outside of an emotional context with overall equivocal results (Barkataki et al., 2008; Joyal et al., 2007). Impaired reward processing with corresponding neural deficits were observed as well in schizophrenia (Meyer-Lindenberg & Bullmore, 2010; Radua et al., 2015) and proposed to be a mechanism for aggression (Bertsch et al., 2020; Fanning et al., 2017; Stahl, 2014). However, the sole study to include positive emotional cues did not analyze them separately from other stimuli (García-Martí et al., 2013). These elements are

important to investigate in order to better understand the neurobiology of aggressive behaviors in this patient population and as basis for potential future interventions (Lamsma, Mackay & Fazel, 2017).

## 1.6 Objectives

The objectives of this dissertation were to investigate the neurocognitive basis of processes posited to be involved in the emergence of aggressive behaviors in individuals with schizophrenia. To this end, we targeted emotion processing, cognitive control, and reward processing using task-based functional magnetic resonance imaging, large samples, appropriate control groups, and a uniform criterion for aggression. All studies were cross-sectional.

In the first study, we set out to assess the neurofunctional alterations in men with schizophrenia and a history of violent behavior using an emotional processing task based on standardized affective photographs depicting negative, positive, and neutral content. Our hypothesis was that the neural processing of emotional stimuli, particularly negative, should be dysregulated in violent men with schizophrenia.

The second study aimed to expand on the previous results by identifying disrupted task-based functional connectivity within the emotional-salience network during negative emotion processing in the same sample as the first study. Based on the few resting-state functional connectivity results, we hypothesized a disrupted fronto-limbic connectivity specific to the group of men with a history of violence.

The third study aimed to investigate the interaction between negative emotion processing and inhibitory control among men with schizophrenia and a history of violence using a new sample of participants. To this end, we employed an affective Go-NoGo task utilizing angry and neutral faces. We hypothesized a failure to recruit regions involved in cognitive control during

motor inhibition specifically in the context of emotional stimuli in men with a history of violence.

The fourth study aimed to investigate the dysregulation of reward system and its association with violence in schizophrenia using the same sample of men as the third study. We hypothesized risk related heightened sensitivity to reward in men with schizophrenia and a history of violence.

# 2 Anterior cingulate hyper-activations during negative emotion processing among men with schizophrenia and a history of violent behavior

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**Abstract**

**Background:** Evidence suggests a 2.1–4.6 times increase in the risk of violent behavior in schizophrenia compared to the general population. Current theories propose that the processing of negative emotions is defective in violent individuals and that dysfunctions within the neural circuits involved in emotion processing are implicated in violence. Although schizophrenia patients show enhanced sensitivity to negative stimuli, there are only few functional neuroimaging studies that have examined emotion processing among men with schizophrenia and a history of violence. **Objective:** The present study aimed to identify the brain regions with greater neurofunctional alterations, as detected by functional magnetic resonance imaging during an emotion processing task, of men with schizophrenia who had engaged in violent behavior compared with those who had not. **Methods:** Sixty men were studied; 20 with schizophrenia and a history of violence, 19 with schizophrenia and no violence, and 21 healthy men were scanned while viewing positive, negative, and neutral images. **Results:** Negative images elicited hyperactivations in the anterior cingulate cortex (ACC), left and right lingual gyrus, and the left precentral gyrus in violent men with schizophrenia, compared to nonviolent men with schizophrenia and healthy men. Neutral images elicited hyperactivations in the right and left middle occipital gyrus, left lingual gyrus, and the left fusiform gyrus in violent men with schizophrenia, compared to the other two groups. **Discussion:** Violent men with schizophrenia displayed specific increases in ACC in response to negative images. Given the role of the ACC in information integration, these results indicate a specific dysfunction in the processing of negative emotions that may trigger violent behavior in men with schizophrenia.

**Keywords**: schizophrenia, violence, negative emotions, salience, anterior cingulate cortex, fMRI

## Introduction

According to the World Health Organization (2015), over 21 million people worldwide suffer from schizophrenia. Of particular concern is the evidence showing an increased risk of aggressive and violent behavior (severe assaults, attempted murder, homicide) among people with schizophrenia compared to the general population (Fazel et al., 2009; Fazel et al., 2014; Grann, Danesh & Fazel, 2008; Swanson et al., 1990; Volavka & Citrome, 2011). Although most people with schizophrenia are not violent (Silverstein et al., 2015; Walsh et al., 2004), individuals suffering from schizophrenia were found to be 2.1–4.6 times more likely to commit a violent crime or engage in violent behavior than the general population, even when taking into account socioeconomic status (SES), comorbid substance use, and personality disorders (Brennan, Mednick & Hodgins, 2000; Fazel et al., 2009; Short et al., 2013). In addition to promoting stigmatization and victimization of all persons with mental health problems (Hodgins, 2008), violent behavior by persons with schizophrenia has important consequences for the health and criminal justice systems, as shown by increasing numbers of forensic hospitals, longer periods in hospital (Dumont et al., 2012; Tulloch, Fearon & David, 2008), and increased rates of incarceration (Hodgins et al., 2007), all of which increase costs. Given that these consequences added to the suffering of the victims, their families, and the perpetrators, it is imperative to identify the neural mechanisms underlying violence in schizophrenia. A better understanding of these mechanisms would allow the development of effective interventions to prevent violent behavior.

Current theories propose that the processing of negative emotions (fear, anger) is defective in violent individuals (Kumari, Das, et al., 2009; Roberton, Daffern & Bucks, 2012). In fact, emotional instability was observed in adult offenders (Roberton, Daffern & Bucks, 2014;

Tager, Good & Brammer, 2010), as well as maladaptive coping with negative affect (Roberton et al., 2012) and oversensitivity to negative stimuli (Chan, Raine & Lee, 2010) has been reported in aggressive men. Moreover, the processing of negative emotions, especially anger, was shown to be a factor in precipitating violent behavior and aggression (Chereji, Pintea & David, 2012; Reagu et al., 2013). As the processing of negative emotions is important in violence, some postulates about the neural underpinnings of violent behavior have been founded in the literature of emotion processing. Considering that negative emotions are processed by a system involving the orbitofrontal cortex, amygdala, and anterior cingulate cortex (ACC), it has been proposed that dysfunctions within this system might be implicated in violence and aggression (Davidson, Putnam & Larson, 2000). Neuroimaging studies of violent individuals have generally supported this assumption (Rosell & Siever, 2015). Given the association between negative affect (anger) and violent behavior in psychotic disorders (Reagu et al., 2013), similar abnormalities in the amygdala–orbitofrontal system might be expected in violent men with schizophrenia (SCZ+V) as in violent men who do not have psychosis (Joyal et al., 2007; Naudts & Hodgins, 2006). However, such neural mechanisms have been investigated to a considerably lesser extent among SCZ+V men.

More neuroimaging studies have investigated structural than functional neural markers of violent behavior among people with schizophrenia. Among SCZ+V, studies have reported reduced brain volumes in the hippocampus (Barkataki et al., 2006; Kumari, Barkataki, et al., 2009; Yang et al., 2010), parahippocampus (Yang et al., 2010), amygdala (Wong et al., 1997), ACC (Kumari et al., 2014), orbitofrontal cortex (Kumari, Barkataki, et al., 2009), cerebellum and supramarginal gyrus (Puri et al., 2008), and increased gray matter volumes in the putamen (Barkataki et al., 2006). Men with schizophrenia and a history of conduct disorder prior to age

15 have been shown to display increased gray matter volumes in the hypothalamus, right precuneus, and right inferior parietal cortex (Schiffer et al., 2013). Moreover, men with schizophrenia and high levels of aggressive behavior displayed larger orbitofrontal cortex (Hoptman et al., 2005) and caudate volumes (Hoptman et al., 2006). To some extent, these structural gray matter alterations occur primarily in the frontal cortex and limbic system where emotion processing dysfunctions have been detected among SCZ+V (Hoptman & Antonius, 2011; Naudts & Hodgins, 2006; Soyka, 2011). However, the currently available results are not consistent.

There are few functional neuroimaging studies that have examined emotion processing among SCZ+V. Relative to men with SCZ with low psychopathic traits, SCZ patients characterized by high levels of psychopathic traits showed blunted amygdala responses to fearful faces (Dolan & Fullam, 2009). Relative to nonpsychotic individuals diagnosed with antisocial personality disorder, SCZ+V displayed greater activity in the thalamus and the caudate nucleus in response to threat stimuli (Kumari, Das, et al., 2009). Finally, Hoptman et al. (2009) reported reduced functional connectivity at resting state between the amygdala and prefrontal regions in SCZ+V. Overall, these results tentatively suggest that abnormalities in the amygdala–orbitofrontal system might be expected among SCZ+V as in violent men without psychosis (Naudts & Hodgins, 2006). However, these studies are limited by small sample sizes and/or lack of adequate comparison groups, as well as omission of positive emotions from the investigated affects. Even though most theories regarding emotion processing in violence concern negative affect (Davidson et al., 2000), examining the processing of positive stimuli could be informative as studies have found reward-processing to be impaired in schizophrenia (Gold et al., 2008) and violent individuals to be especially sensitive to immediate reward

(Cherek et al., 1997). Of further interest, Cohen and Minor (2010) have noted that schizophrenia is associated with an aversion to neutral stimuli. Functional magnetic resonance imaging (fMRI) findings show that persons with schizophrenia assign abnormal salience to neutral material (Hall et al., 2008; Lakis & Mendrek, 2013; Potvin et al., 2015). Therefore, it is also important to explore the neural response to neutral stimuli when examining emotional processing in SCZ+V.

Overall, knowledge of emotion processing in SCZ+V is scarce and inconclusive. Using adequate control groups, we sought to identify brain regions with neurofunctional alterations among SCZ+V compared to men with schizophrenia who have no history of violence (SCZ-V) and healthy controls, during an fMRI emotion processing task. Responses to negative, positive, and neutral emotions were assessed.

## Methods

### *Participants*

Thirty-nine male outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria; age 18–55 years) were recruited from forensic and general psychiatric hospitals. They were divided into two groups: 20 SCZ+V and 19 SCZ-V. In accordance with the MacArthur study, serious violence was defined as a history of armed aggression resulting in injuries or death (Monahan et al., 2001). Antecedents of serious violence were assessed based on clinical interview (Structured Clinical Interview for DSM-IV; Spitzer et al. (1992)), self-reports (MacArthur Community Violence Instrument; Monahan et al. (2001)), and clinical files. All patients were stabilized on antipsychotic medication that had not changed within the last 2 months. Antipsychotic dosage was calculated using chlorpromazine equivalents (Woods, 2003). Symptom severity was evaluated with the Positive and Negative Syndrome Scale (Kay, Fiszbein

& Opler, 1987), which yield five subscores (i.e., positive, negative, disorganization/cognitive, excitation, depression) according to Lindenmayer, Grochowski and Hyman (1995) five-factor model of schizophrenia. Urine drug screenings were administered.

The control group included 21 men with no history of violent behavior. Controls were screened with the nonpatient edition of the Structured Clinical Interview for DSM-IV (Spitzer et al., 1992).

All participants were free of concomitant neurological disorders and substance use disorders (lifetime, for controls; in the last 12 months, for SCZ+V and SCZ-V). No participant had an IQ lower than 70 or MRI contraindications. Parental SES was assessed according to the National Occupational Classification (Human Resources and Skills Development Canada, 2001). Finally, as in prior studies on violence (Harris, Hilton & Rice, 2011), we calculated the number of DSM-IV diagnostic criteria for antisocial personality disorder (Spitzer et al., 1992) that were met by each participant. The score ranged from no criterion to seven criteria.

*Ethical approval*

The patients were recruited by clinical staff that they knew. After having the study explained to them, all participants signed a consent form agreeing to interviews, an MRI, and the patients consented to giving access to their medical and criminal files. The study was approved by the local ethics committees from the Regroupement de Neuroimagerie du Québec, the Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal, and the Institut Philippe-Pinel de Montréal.

*Experimental procedure and task*

During fMRI, participants viewed blocks of emotionally positive, negative, and neutral pictures from the International Affective Picture System (IAPS) (Lang, Bradley & Cuthbert, 2008). These pictures were matched for content (people, animals, landscapes), visual complexity and color, and grouped based on valence and arousal intensity (using the IAPS normative data), resulting in five experimental conditions: high arousal/positive, high arousal/negative, low arousal/positive, low arousal/negative, and neutral. Each condition was presented in separate blocks lasting 48.5 seconds, interceded by 16-second rest periods. To ensure that participants attended to the images, they were asked to press a button whenever they saw a person in the picture. Each block contained ten images of one specific experimental condition, and each block type (high arousal/positive, high arousal/negative, low arousal/positive, low arousal/negative) was repeated two times (except the neutral block, which was repeated four times). Each picture appeared for 3,000 ms followed by a blank screen with a fixation point for an average of 1.75 seconds (average interstimulus interval 4.75 seconds). The order of presentation of blocks was pseudorandomized. At the end of the fMRI session, participants were asked to rate [Addendum: the subjective arousal elicited by] the photographs in each block, on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime).

*Neuroimaging acquisition parameters*

Whole-brain fMRI was performed using an echoplanar imaging sequence measuring blood oxygenation level-dependent (BOLD) signal (TR =3,000 ms; TE =30 ms; FA =90°; matrix =64×64; voxel size =3.5 $mm^3$; 41 slices). The functional slices were oriented in transverse plane and were angled to be parallel to the AC–PC line. An inline retrospective motion correction

algorithm was employed while the echoplanar images were acquired. Individual high-resolution coplanar anatomical images were also acquired during the same scanning session (three-dimensional, spoiled gradient echo sequence; TR =19 ms; TE =4.92 ms; FA =25°; matrix size =256×256; voxel size =1 $mm^3$; 176 slices).

*Analysis of fMRI data*

fMRI data was analyzed with Brain Voyager QX software (Brain Innovation, Maastricht, the Netherlands). Functional images were slice-time-corrected, corrected for motion artifacts (≤2 mm; all fMRI images were usable), high-pass-filtered (two cycles per time course), coregistered to the corresponding anatomical image, spatially normalized to the Talairach space (Talairach & Tournoux, 1988), and spatially smoothed with a 3D isotropic Gaussian kernel (8 mm FWHM).

We used a standard peak detection approach and a general linear model to identify the cerebral changes associated with emotion processing. Five predictors of interest, corresponding to the experimental conditions/blocks, were convolved with the hemodynamic response function estimated using the double-γ model (Boynton et al., 1996), and a first-order autoregression model was used to account for serial correlations. Initially, a first-level analysis was performed to investigate individual brain activation maps associated with the primary contrasts of interest ([High Negative + Low Negative] > Neutral; orthogonal) ([High Positive + Low Positive] > Neutral; orthogonal). The (Neutral > Rest) contrast was also examined. A second-level random-effects model was then computed to investigate the pattern of activations during emotion processing comparing the three groups (Penny & Holmes, 2007). Between-group differences in clinical variables were considered as covariates in fMRI group comparisons.

The statistical threshold for significance was determined by Monte Carlo simulation (Ward, 2000). Assuming a voxel-level threshold of $P<0.001$ (10,000 simulations), a cluster size of 343 $mm^3$ was required to correct for multiple comparisons at $P<0.05$. When relevant, we identified common activations between contrasts by performing spatial conjunction analyses, using the "Volume of Interest" option of Brain Voyager. For each cluster found to significantly differ between groups in the spatial conjunction analyses, the individual changes in BOLD signal (i.e., β-values) were extracted and used to visually display results and to perform correlation analyses between regional BOLD responses and clinical variables (e.g., emotional ratings, antisocial traits) within subgroups.

*Statistical analysis of the clinical data*

For continuous data, between-group differences were examined using analyses of variances. Pair-wise comparisons were performed using Tukey's HSD tests. For dichotomic data, $\chi^2$ tests were used. For pair-wise comparisons, Bonferroni correction was applied.

## Results

*Characteristics of the participants*

Table 1 presents comparisons of the three groups of participants. No differences were detected in age, handedness, and ratings of positive and negative images (all *P*-values >0.05). SCZ+V had lower parental SES than controls ($P$=0.013). SCZ participants, with and without violent behavior, did not differ as to primary diagnoses (schizophrenia vs schizoaffective disorder), age of onset, illness duration, negative symptoms, chlorpromazine equivalents, and the proportion of SCZ patients treated with clozapine (all $P$>0.05). However, SCZ+V presented fewer positive and disorganized symptoms than SCZ-V ($P$<0.010 and $P$=0.010, respectively). Finally, SCZ+V assigned more emotional significance [Addendum: (i.e., subjective arousal)] to neutral images than controls, but this result did not achieve significance ($P$=0.07), and there was no significant difference between schizophrenia subgroups ($P$>0.05).

*Groups comparisons of neural activity during presentation of negative pictures*

As presented in Table 2, for the Negative minus Neutral contrast, relative to SCZ-V, SCZ+V showed increased activations in the lingual gyrus, the right middle frontal gyrus, the right inferior frontal gyrus, the bilateral globus pallidus, the right precuneus, the anterior and mid-cingulate gyrus, and the left precentral gyrus. Relative to controls, SCZ+V showed increased activations in the right fusiform gyrus, the right superior frontal gyrus, the anterior cingulate gyrus, the left lingual gyrus, and the left precentral gyrus. Finally, relative to controls, SCZ-V had decreased activations in temporal, parietal, paralimbic, and cerebellar regions (Table 2).

Table 1. Characteristics of participants

| | SCZ+V (n=20) | SCZ-V (n=19) | Healthy controls (n=21) | Significance |
|---|---|---|---|---|
| Age, mean (SE) | 30.0 (1.6) | 31.4 (1.7) | 30.9 (1.7) | $F$=0.2; $p$=0.842 |
| Parental SES, (SE) | 3.4 (0.3) | 2.9 (0.1) | 2.4 (0.2) | ***F*=4.4; p=0.017** * |
| Handedness, % right | 90.0 | 78.9 | 85.7 | $\chi^2$=4.0; $p$=0.400 |
| Diagnoses | 6 SA | 3 SA | - | $\chi^2$=1.1; $p$=0.292 |
| Age of onset (SE) | 21.0 (1.1) | 20.8 (0.8) | - | $F$=0.01; $p$=0.909 |
| Duration of illness (SE) | 9.5 (4.8) | 10.6 (7.5) | - | $F$=0.3; $p$=0.609 |
| PANSS | | | | |
| Positive | 9.1 (2.4) | 12.1 (0.8) | - | ***F*=9.6; *p*<0.010** |
| Negative | 12.9 (5.5) | 15.5 (1.3) | - | $F$=2.0; $p$=0.166 |
| Disorganization | 6.8 (1.9) | 8.5 (0.4) | - | ***F*=7.4; *p*=0.010** |
| Excitation | 8.3 (3.0) | 7.5 (0.6) | - | $F$=0.6; $p$=0.433 |
| Depression | 6.5 (2.3) | 7.1 (0.4) | - | $F$=0.7; $p$=0.416 |
| Ratings | | | | |
| Positive images (SE) | 4.6 (0.3) | 4.8 (0.3) | 4.4 (0.3) | $F$=0.3; $p$=0.784 |
| Negative images (SE) | 5.3 (0.4) | 5.3 (0.3) | 5.1 (0.3) | $F$=0.5; $p$=0.603 |
| Neutral images (SE) | 2.4 (0.4) | 2.1 (0.5) | 1.2 (0.3) | ***F*=2.8; *p*=0.072** * |
| Chlorpromazine Equivalents, mg, (SE) | 846.9 (170.7) | 654.4 (74.7) | - | $F$=1.1; $p$=0.309 |
| Clozapine (n) | 6 | 9 | - | $\chi^2$=1.2; $p$=0.265 |

Note: Significant results are shown in bold ($P$<0.05). *SCZ-V > controls ($P$<0.05).
Abbreviations: PANSS, Positive and Negative Syndrome Scale; SA, schizoaffective disorder; SCZ+V, schizophrenia with violent behavior; SCZ-V, schizophrenia without violent behavior; SE, standard error; SES, socioeconomic status (a higher number indicates a lower SES).

Table 2. Between-group differences in brain activations during viewing of negative emotion pictures

| Brain regions | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Schizophrenia + violence > schizophrenia | | | | | | |
| Lingual gyrus, extending to the left middle occipital, the bilateral cerebellum, the right middle temporal and the left fusiform) | 18 | 0 | -85 | -2 | 98791 | 5.8 |
| Right middle frontal gyrus | 10 | 33 | 53 | 10 | 1217 | 3.8 |
| Right inferior frontal gyrus/ superior temporal gyrus | 13 / 38 | 33 | 8 | -11 | 903 | 4.3 |
| Right globus pallidus | – | 24 | -16 | -8 | 1027 | 3.7 |
| Right precuneus | 7 | 21 | -73 | 37 | 728 | 4.0 |
| Anterior cingulate gyrus | 32 | 3 | 38 | -2 | 2159 | 4.1 |
| Mid-cingulate gyrus | 24 | 3 | -4 | 31 | 1027 | 4.1 |
| Left globus pallidus | – | -21 | -13 | -5 | 2052 | 4.5 |
| Left precentral gyrus | 6 | -42 | -4 | 31 | 1828 | 4.1 |
| Schizophrenia > schizophrenia + violence | None | | | | | |
| Controls > schizophrenia + violence | None | | | | | |
| Schizophrenia + violence > control | | | | | | |
| Right fusiform gyrus, extending to the right lingual gyrus and the right inferior temporal) | 19 | 36 | -73 | -8 | 12498 | 5.5 |
| Right superior frontal gyrus | 9 | 15 | 38 | 40 | 362 | 3.8 |
| Anterior cingulate gyrus | 32 | 3 | 44 | 4 | 1031 | 4.0 |
| Left lingual gyrus | – | -18 | -79 | -17 | 1852 | 4.2 |
| Left precentral gyrus | 6 | -39 | -1 | 34 | 1389 | 4.4 |
| Controls > schizophrenia | | | | | | |
| Right superior temporal gyrus | 38 | 33 | 17 | -29 | 402 | 4.4 |
| Cerebellum (tonsil) | – | -6 | -37 | -41 | 1619 | 4.4 |
| Posterior cingulate gyrus | 29 | -3 | -37 | 13 | 6264 | 4.5 |
| Left cerebellum (tonsil) | – | -30 | -49 | -38 | 614 | 3.7 |
| Left hippocampus | – | -33 | -31 | -8 | 1905 | 3.9 |
| Left inferior parietal | 40 | -42 | -52 | 46 | 2579 | 4.2 |
| Left superior temporal gyrus | 39 | -48 | -52 | 22 | 765 | 3.9 |
| Schizophrenia > controls | None | | | | | |

Notes: * T-value of the highest peak within the cluster to significantly differ between groups; P<0.001.
Abbreviation: BA, Brodmann area.

*Conjunction analyses*

Since SCZ+V had increased activations compared to SCZ-V and controls, spatial conjunction analyses were performed to identify neural differences common to both group comparisons. As illustrated in Table 3, spatial conjunction analyses revealed four intersections between the "SCZ+V minus SCZ-V" and the "SCZ+V minus Controls" contrasts, namely the right lingual gyrus, the left lingual gyrus, the anterior cingulate gyrus, and the left precentral gyrus (Figure 1). Hyperactivations in these clusters remained significant after controlling for positive and disorganized symptoms, clozapine, and parental SES. Among participants with SCZ, no significant correlations were observed between regional brain activity and subjective [Addendum: arousal] ratings of negative images and antisocial personality traits (all *P*-values >0.05).

Table 3. Spatial conjunction analyses for the Negative minus Neutral contrast

| Brain regions | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Schizophrenia + violence > schizophrenia and controls | | | | | | |
| Right lingual gyrus | 18 | 3 | -85 | -2 | 7471 | 5.6 |
| Left lingual gyrus | 18 | -15 | -82 | -17 | 1807 | 5.1 |
| Anterior cingulate gyrus | 24 | 3 | 38 | 0 | 320 | 4.0 |
| Left precentral gyrus | 6 | -42 | -4 | 31 | 980 | 4.1 |

Notes: * T-value for the highest peak within the cluster to significantly differ between groups; *P*<0.001. Abbreviation: BA, Brodmann area.

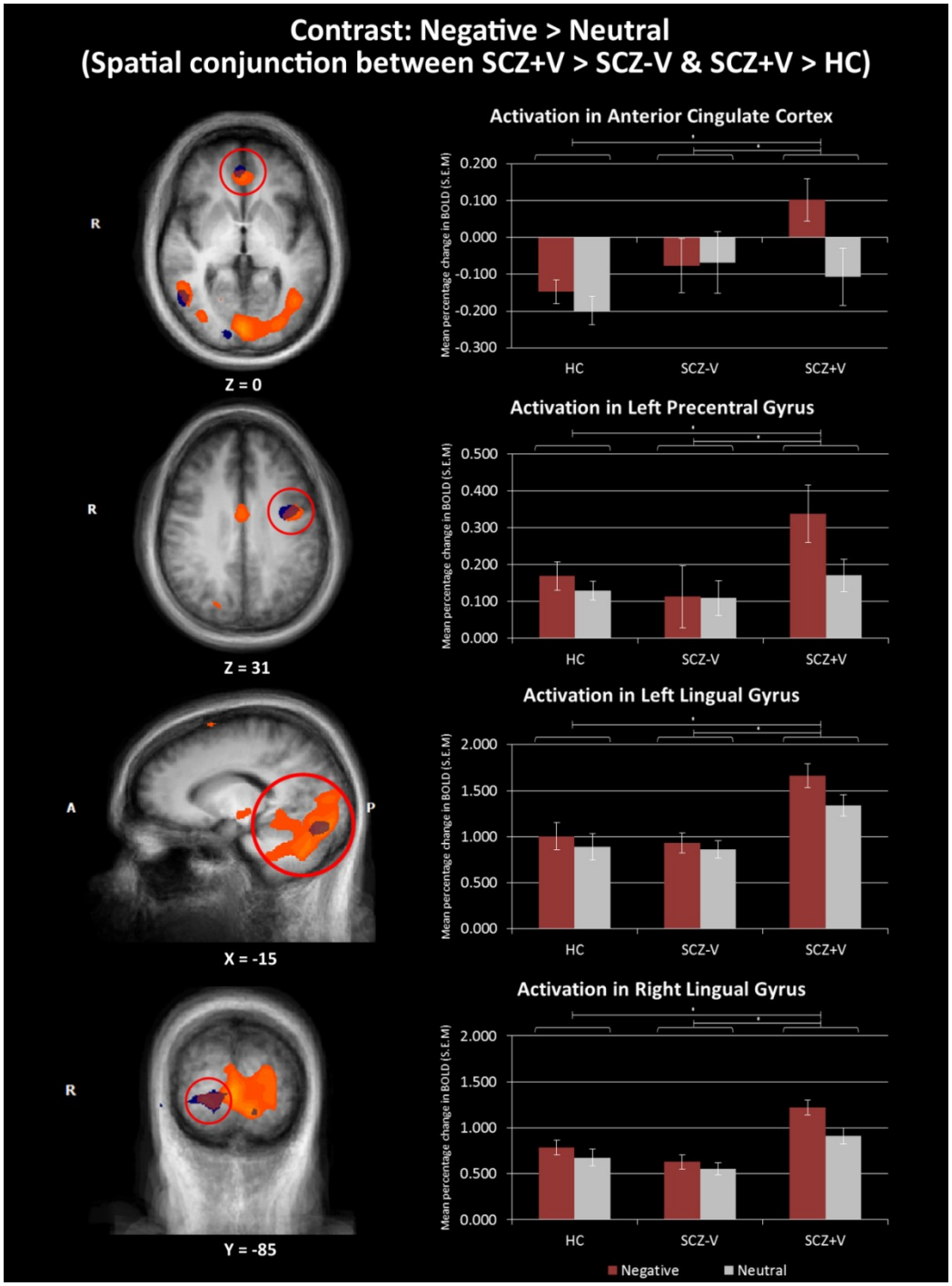


Figure 1. Spatial conjunction analyses for the Negative minus Neutral contrast.

Notes: The Figure displays the four intersections between the [SCZ+V>SCZ-V] and the [SCZ+V>HC] comparisons (*$T$-value for the highest peak within the cluster to significantly differ between groups; $P$<0.001; cluster-threshold: 343mm$^3$). Results for the SCZ+V>HC comparison are displayed in blue, and for the SCZ+V>SCZ-V comparison, in orange. Bar graphs refer to means and SEMs.

Abbreviations: A, anterior; BOLD, blood oxygen level dependent; HC, healthy controls; P, posterior; R, right; SCZ+V, schizophrenia patients with violent behavior; SCZ-V, schizophrenia patients without violent behavior; SEM, standard error of the mean.

*Groups comparisons of neural activity during presentation of positive pictures*

For the Positive minus Neutral contrast, no differences were observed between SCZ+V and SCZ-V, or between SCZ-V and controls. Relative to controls, SCZ-V had decreased activations in the left lingual gyrus/cerebellar culmen ($x$ =-15; $y$ =-31; $z$ =-14; $t$ =3.8; $P$<0.001; 571 voxels). Among the participants with SCZ, no significant correlations were observed between regional brain activity and subjective ratings of positive images, and antisocial personality traits (all $P$-values >0.05).

*Groups comparisons of neural activity during presentation of neutral pictures*

As presented in Table 4, for the Neutral minus Rest contrast, relative to SCZ-V, SCZ+V showed increased activations in the right inferior temporal gyrus, the bilateral middle occipital gyrus, the medial frontal gyrus, and the left cerebellar tuber. Relative to controls, SCZ+V displayed increased activations in the right middle frontal gyrus, the right and medial superior frontal gyrus, the bilateral superior temporal gyrus, the right superior parietal gyrus, the right cuneus, the left caudate nucleus, the left postcentral gyrus, the left lingual gyrus, and the left inferior occipital gyrus. Relative to controls, SCZ-V showed increased activations in the left inferior parietal gyrus (Table 3).

Table 4. Between-group differences in brain activations during viewing of neutral images

| Brain region | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Schizophrenia + violence > schizophrenia | | | | | | |
| Right inferior temporal gyrus | 37 | 57 | -46 | -23 | 462 | 4.1 |
| Left middle occipital gyrus, extending to the right middle occipital, the lingual gyrus and the bilateral fusiform gyrus) | 19 | -36 | -82 | 4 | 42793 | 5.3 |
| Medial frontal gyrus | 11 | 0 | 44 | -17 | 355 | 4.0 |
| Left cerebellar tuber | – | -57 | -49 | -29 | 496 | 3.9 |
| Schizophrenia > schizophrenia + violence | None | | | | | |
| Controls > schizophrenia + violence | None | | | | | |
| Schizophrenia + violence > Controls | | | | | | |
| Right middle frontal gyrus | 9 | 60 | 11 | 37 | 15541 | 4.9 |
| Right superior temporal gyrus | 38 | 42 | 17 | -23 | 904 | 3.7 |
| Right superior parietal | 7 | 30 | -55 | 46 | 2987 | 4.3 |
| Right cuneus | 18 | 21 | -91 | 16 | 1080 | 3.8 |
| Left caudate nucleus | – | -15 | 17 | -2 | 5679 | 4.6 |
| Superior frontal gyrus | 9 | -3 | 59 | 28 | 1206 | 3.9 |
| Left postcentral gyrus | 40 | -48 | -31 | 52 | 14975 | 5.2 |
| Left lingual gyrus | 18 | -12 | -82 | -20 | 1031 | 3.8 |
| Left inferior occipital | 19 | -48 | -82 | -5 | 8061 | 5.9 |
| Left fusiform gyrus | 19 | -24 | -67 | -17 | 408 | 4.6 |
| Left superior temporal gyrus | 38 | -39 | 5 | -20 | 1393 | 3.8 |
| Controls > schizophrenia | None | | | | | |
| Schizophrenia > controls | | | | | | |
| Left inferior parietal gyrus | 40 | -36 | -46 | 49 | 1007 | 4.2 |

Notes: **T*-value for the highest peak within the cluster to significantly differ between groups; $p<0.001$.
Abbreviation: BA, Brodmann area.

*Conjunction analyses*

As illustrated in Table 5, spatial conjunction analyses revealed four intersections between the "SCZ+V minus SCZ" and the "SCZ+V minus Controls" contrast, namely the right middle occipital gyrus, the left lingual gyrus, the left middle occipital gyrus, and the left fusiform gyrus (Figure 2). Hyperactivations in these clusters remained significant after controlling for positive and disorganized symptoms, clozapine, and parental SES. Among participants with SCZ, no

significant correlations were observed between regional brain activity and subjective ratings of neutral images, and antisocial personality traits (all $P>0.05$).

Results of within-group contrasts (Negative > Neutral; Positive > Neutral) are provided in Tables S1 and S2.

Table 5. Spatial conjunction analyses for the Neutral minus Rest contrast

| Brain regions | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Schizophrenia + violence > schizophrenia and controls | | | | | | |
| Right middle occipital gyrus | 18 | 24 | -94 | 10 | 944 | 3.9 |
| Left lingual gyrus | 18 | -9 | -88 | -17 | 337 | 4.0 |
| Left middle occipital gyrus | 19 | -37 | -82 | 4 | 4454 | 5.2 |
| Left fusiform gyrus | 19 | -24 | -64 | -14 | 123 | 4.0 |

Notes: **T*-value for highest peak within the cluster to significantly differ between groups; $p<0.001$.
Abbreviation: BA, Brodmann area.

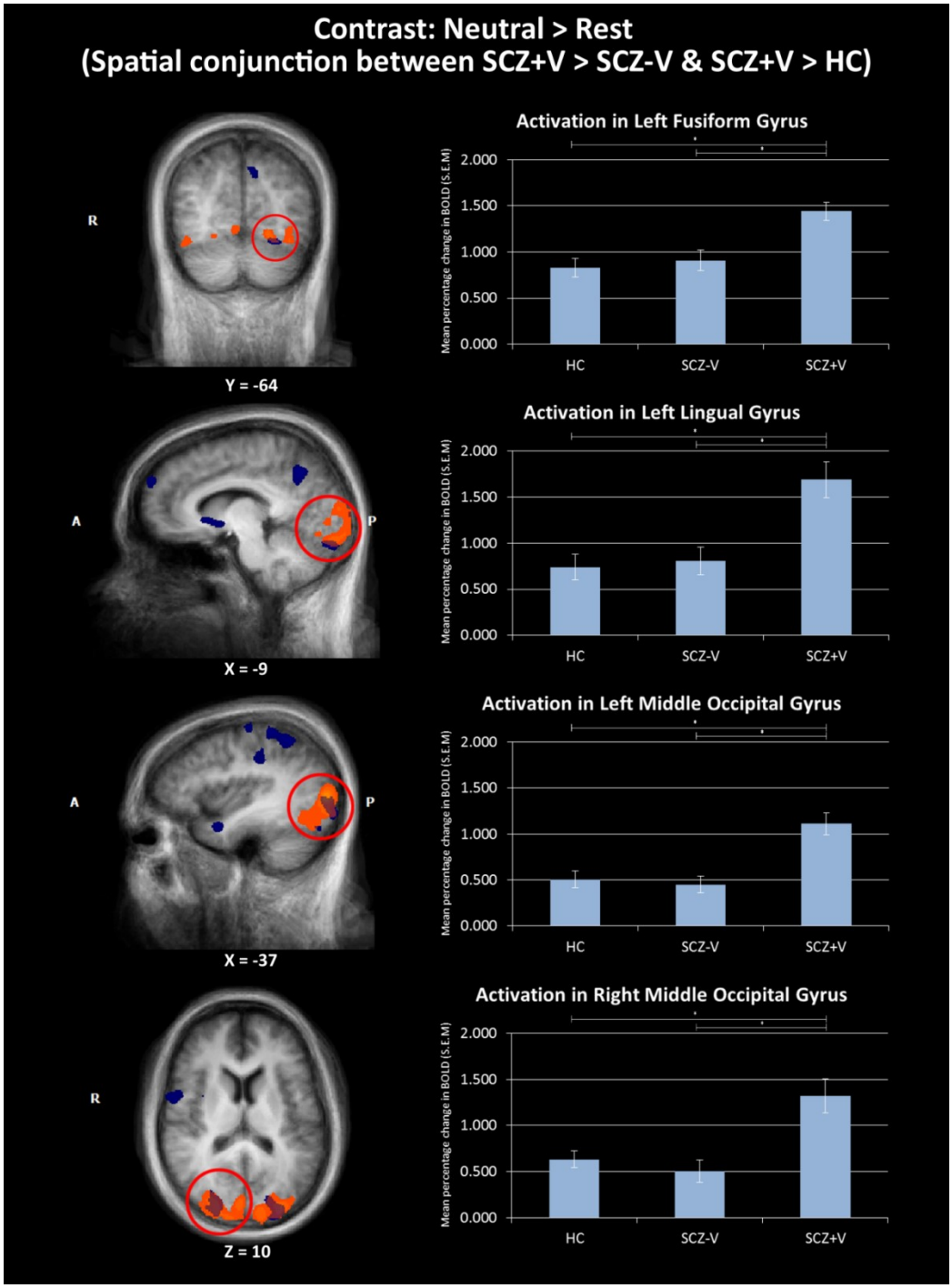


Figure 2. Spatial conjunction analyses for the Neutral minus Rest contrast.

Notes: The figure displays the four intersections between the [SCZ+V>SCZ-V] and the [SCZ+V>HC] comparisons (*$T$-value for the highest peak within the cluster to significantly differ between groups; $P$<0.001; cluster-threshold: 343mm$^3$). Results for the SCZ+V>HC comparison are displayed in blue, and for the SCZ+V>SCZ-V comparison, in orange. Bar graphs refer to means and SEMs.

Abbreviations: A, anterior; BOLD, blood oxygen level dependent; HC, healthy controls; P, posterior; R, right; SCZ+V, schizophrenia patients with violent behavior; SCZ-V, schizophrenia patients without violent behavior; SEM, standard error of the mean.

**Discussion**

This is the first study to identify neural alterations in the processing of negative and neutral emotions among men with schizophrenia and a history of violent behavior as compared to men with schizophrenia and no history of violent behavior and healthy nonviolent men. Negative pictures elicited hyperactivations in SCZ+V relative to SCZ-V and healthy controls in the ACC, the right and left lingual gyrus, and the left precentral gyrus, regardless of arousal intensity. During viewing of neutral stimuli, hyperactivations in SCZ+V were relative to SCZ-V and controls in the left and right middle occipital gyrus, the left lingual gyrus, and the left fusiform gyrus. To our knowledge, this is the first study to report that SCZ+V attribute a higher intensity of experienced emotion to neutral stimuli than healthy controls, a result consistent with similar observations previously made in nonpsychotic individuals with antisocial behavior (Dadds et al., 2006). Regarding positive stimuli processing, we did not observe activations that distinguished SCZ+V from either SCZ-V or healthy controls. However, when viewing positive emotion pictures, SCZ+V showed decreased activations in the left lingual gyrus compared to healthy controls.

The most important finding of the current study is the increase in the ventral ACC reactivity to negative stimuli specifically observed in SCZ+V. The cingulate cortex is crucial in integrating input from many different sources (Bush, Luu & Posner, 2000), and recent studies suggest that the ACC, subdivided into ventral/rostral/affective and mid/dorsal/cognitive regions, is key for the integration of negative affect and cognitive control (Amodio & Frith, 2006; Bush et al., 2000; Shackman et al., 2011). Indeed, a meta-analysis of fMRI studies suggested that ventral ACC is associated with the generation of emotion, and the dorsal ACC with emotion regulation (Kober et al., 2008). Furthermore, due to important connections with both the

amygdala and the orbitofrontal cortex, the ACC appears to be involved in violent behavior as well (Rosell & Siever, 2015). Considering the role of the ACC in emotion processing (Davidson et al., 2000; Shackman et al., 2011), the results of the current study suggest that ventral ACC dysfunctions are associated with negative stimuli processing in SCZ+V. A meta-analysis that included 450 SCZ-V reported reduced activity in ACC in relation to emotion processing and emotional experience (Taylor et al., 2012). These latter results might reflect a hyperactivation of the ACC during the viewing of emotionally neutral stimuli, as SCZ-V have been reported to assign abnormal salience to neutral stimuli (Hall et al., 2008; Lakis & Mendrek, 2013; Potvin et al., 2015). Nevertheless, the results of the current study show that ACC hyperactivations distinguished SCZ+V from the two other groups. Based on the extant literature, dysfunctions in the prefrontal lobe, amygdala, or subcortical nuclei might have been expected in SCZ+V (Dolan & Fullam, 2009; Hoptman et al., 2009; Kumari, Das, et al., 2009). Negative stimuli did elicit activations in the amygdala within the SCZ+V group, although they were not significantly different from the activations elicited in the other two groups. Given that the amygdala is associated with the automatic detection of threat (Öhman, 2005) and that the ACC is associated with the integration of information (Bush et al., 2000), our results might indicate that there is a dysfunction in more elaborate emotion processing among SCZ+V. Evidence shows that negative emotions may be a factor in precipitating violent behavior. The current findings provide a potential mechanistic explanation for this documented clinical observation (Davidson et al., 2000).

We also observed a potential influence of image valence on the activity of regions associated with early visual detection (lingual gyrus, fusiform gyrus, middle occipital gyrus) and movement planning (precentral gyrus) in SCZ+V. Activations in the visual cortex during

the viewing of emotional stimuli have been frequently reported (Phan et al., 2002). It has been suggested that early processing might be enhanced as a means of providing advantage in information processing to specific emotional stimuli (aversive, appetitive) (Murphy, Nimmo-Smith & Lawrence, 2003). It is noteworthy that negative and neutral stimuli elicited hyperactivations in the left lingual gyrus in SCZ+V relative to SCZ-V and healthy controls, whereas positive stimuli elicited a hypoactivation of the same region in SCZ+V compared to healthy controls. This pattern, specific to SCZ+V, appears to be an attentional bias in early visual detection as a function of valence, which might indicate that visual emotional stimuli are processed differently in this population. Further studies are needed to investigate whether, in fact, this effect is associated with violence. Finally, the hyperactivation of the left precentral gyrus elicited by negative stimuli might indicate an action/motor preparation (Simon et al., 2002).

This study has certain limitations. Participants in both SCZ+V and SCZ-V groups were taking antipsychotic medications, which could confound the results. However, the potential effects of antipsychotics on the neural correlates of emotion processing are highly inconsistent (H Roder et al., 2013; H Roder, Marie Hoogendam & M van der Veen, 2010; Potvin et al., 2015; Stip et al., 2005; Surguladze et al., 2011). Moreover, no group differences were detected in chlorpromazine-equivalent dose, and chlorpromazine equivalents did not correlate with brain activity. Further, the proportions of participants with SCZ receiving clozapine did not differ between groups, and clozapine had no significant influence on results. This lack of effect of clozapine may be explained by the fact that the brain regions found to be altered here (e.g., anterior cingulate and occipital) are not the ones the most consistently affected by clozapine (e.g., striatum) (Mouchlianitis, McCutcheon & Howes, 2016). SCZ+V presented fewer positive

symptoms than SCZ-V. However, our results remained significant when we entered this potential confound in the analyses. Previous studies have shown that elevated levels of positive symptoms are associated with violence (Krakowski & Czobor, 2004; Steinert, 2002). In fact, positive psychotic symptoms constitute the principal factor associated with violence during an acute psychotic episode, as does a long duration of untreated psychosis (Hodgins & Riaz, 2011). Once patients are stabilized on antipsychotic medications and present low levels of positive symptoms (<3 on the Positive and Negative Syndrome Scale), neither violent behavior nor other forms of psychosocial functioning are associated with positive symptoms (Hodgins, Lincoln & Mak, 2009). SCZ+V were characterized by lower parental SES relative to healthy controls, which is consistent with a recent meta-analysis suggesting that low SES might be a risk factor for violence in psychosis (Witt, van Dorn & Fazel, 2013). We performed analyses of covariances and found that parental SES did not influence the main results. In this study, we did not recruit a group of nonpsychotic violent individuals. Even though we did not observe an effect of antisocial personality on our results, the inclusion of a group of nonpsychotic individuals with violent or antisocial behavior would have eased the interpretation of our findings. In nonpsychotic individuals with violent or antisocial behavior, reductions in ACC volumes were reported in some studies, while others have not confirmed these findings (Yang & Raine, 2009). A few functional neuroimaging studies have observed abnormal ACC activations in violent/antisocial and nonpsychotic individuals during emotion processing; however, activations were reduced rather than increased (Kiehl et al., 2001; Pardini & Phillips, 2010; Yang & Raine, 2009). Taken together, the available evidence makes it difficult to determine if our results are explained by an effect of violence or by an interaction between psychosis and violence (Hodgins, Piatosa & Schiffer, 2013). Finally, although IAPS images are well validated

for the study of emotional valence and arousal (Lang et al., 2008), the images present in our study and our experimental design were not optimized to investigate discrete emotions such as anger. The study was characterized by several strengths including relatively large samples of men with schizophrenia who underwent detailed assessments of all disorders including substance use disorders, symptoms, and violent behavior. Finally, objective measures showed that no participant had been using substances prior to the brain scan.

## Conclusion

To conclude, this is the first fMRI study to investigate the processing of positive, negative, and neutral stimuli among men with schizophrenia and a history of violence. A potential bias toward image valence in early visual detection was observed among SCZ+V. More importantly, these men displayed ventral ACC dysfunctions when processing negative stimuli. Given the role of the ACC in information integration, these results potentially indicate a dysfunction in more elaborate processes related to emotions among SCZ+V. Future studies are needed to investigate the influence of discrete emotions (anger) and emotion regulation on the ACC of this population.

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**Disclosure**

The authors report no conflicts of interest in this work.

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**Supplementary Material**

Table S1. Brain activations in each group during negative emotions

| Brain region | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| *Schizophrenia + violence* | | | | | | |
| Negative minus Neutral[a] | | | | | | |
| Left fusiform gyrus, extending to the lingual gyrus, bilateral cerebellum, posterior cingulate, left middle temporal, thalamus, bilateral amygdala / globus pallidus, bilateral inferior frontal gyrus | 19 | -42 | -67 | -14 | 269,855 | 14.4 |
| Medial frontal gyrus, extending to the middle frontal gyrus, anterior cingulate gyrus and left precentral gyrus | 6 | -3 | -20 | 64 | 29,037 | 7.7 |
| Right superior temporal gyrus | 22 | 48 | -7 | -8 | 668 | 4.5 |
| Right sub-gyral temporal | 20 | 39 | -13 | -20 | 466 | 4.8 |
| Mid-cingulate | 24 | -3 | -4 | 31 | 445 | 4.6 |
| Left cerebellum tonsil | | -18 | -28 | -38 | 363 | 4.7 |
| *Schizophrenia* | | | | | | |
| Negative minus Neutral | | | | | | |
| Right fusiform gyrus | 19 | 33 | -79 | -17 | 444 | 4.2 |
| Left fusiform gyrus | 37 | -39 | -58 | -20 | 1,004 | 4.9 |
| *Controls* | | | | | | |
| Negative minus Neutral | | | | | | |
| Brain stem, extending to the bilateral amygdala and the bilateral superior temporal gyri | – | -5 | -23 | -7 | 49,013 | 8.1 |
| Right fusiform gyrus | 37 | 39 | -43 | -11 | 11,359 | 7.8 |
| Left cerebellum tonsil | – | -12 | -40 | -38 | 8,456 | 5.8 |
| Medial frontal gyrus | 9 | 9 | 50 | 19 | 1,357 | 4.8 |
| Posterior cingulate gyrus | 31 | 12 | -43 | 22 | 771 | 4.9 |
| Anterior cingulate gyrus | 24 | 6 | 26 | -5 | 1,330 | 6.0 |
| Left fusiform gyrus | 19 | -36 | -67 | -11 | 22,929 | 8.2 |
| Left middle frontal gyrus | 9 | -45 | 14 | 28 | 1,100 | 4.6 |

Notes: **T*-value for the highest peak of activation with the cluster; $P<0.001$; [a]The contrast Neutral minus Negative revealed no significant clusters of activations within groups.
Abbreviations: BA, Brodmann area.

Table S2. Brain activations in each group during positive emotions

| Brain region | BA | Talairach coordinates | | | Voxels ($mm^3$) | Max *T** |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| *Schizophrenia + violence* | | | | | | |
| Positive minus Neutral | | | | | | |
| Right middle occipital gyrus | 37 | 48 | -67 | -5 | 5,396 | 5.1 |
| Left fusiform gyrus | 37 | -45 | -61 | -20 | 3,015 | 6.3 |
| Neutral minus Positive | | | | | | |
| Right fusiform gyrus | 37 | 27 | -37 | -11 | 953 | 4.1 |
| Left parahippocampal gyrus | 36 | -24 | -40 | -11 | 1,609 | 4.6 |
| Left inferior parietal gyrus | 40 | -39 | -31 | 31 | 1,078 | 4.0 |
| *Schizophrenia* | | | | | | |
| Positive minus Neutral | | | | | | |
| Left fusiform gyrus | 37 | -45 | -64 | -23 | 401 | 4.0 |
| Neutral minus Positive | None | | | | | |
| *Controls* | | | | | | |
| Positive minus Neutral | | | | | | |
| Right middle temporal gyrus | 39 | 42 | -52 | 4 | 9,286 | 7.2 |
| Right amygdala | – | 21 | -10 | -11 | 6,491 | 7.1 |
| Superior frontal gyrus | 9 | -9 | 56 | 28 | 6,182 | 6.9 |
| Precuneus | 7 | 0 | -58 | 31 | 5,951 | 7.1 |
| Anterior cingulate gyrus | 32 | 0 | 38 | -5 | 631 | 4.4 |
| Left middle temporal gyrus | 21 | -51 | -7 | -17 | 14,539 | 7.0 |
| Left middle frontal gyrus | 6 | -36 | 8 | 49 | 467 | 5.1 |
| Left fusiform gyrus | 37 | -39 | -46 | -20 | 1,062 | 4.5 |
| Neutral minus Positive | | | | | | |
| Left precentral gyrus | 6 | -27 | -19 | 52 | 1,178 | 5.5 |

Notes: **T*-value for the highest peak of activation within the cluster; $P<0.001$.
Abbreviation: BA, Brodmann area.

# 3 Violent behavior is associated with emotion salience network dysconnectivity in schizophrenia

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**Abstract**

**Background:** Despite individuals with schizophrenia being at an elevated risk of violence compared to the general population, limited efforts have been invested in investigating the neurobiological etiology explaining the increase. Among the few studies examining functional disruptions pertaining to violent schizophrenia patients using fMRI, only one study has considered functional connectivity. The current state of knowledge does not allow to infer deficits in functional connectivity specific to distinct cognitive/emotional states that have been associated with the emergence of violence in schizophrenia, such as negative emotion processing. This study sought to identify disrupted connectivity among men with schizophrenia and a history of violence (SCZ+V), compared to men with schizophrenia without a history of violence (SCZ-V) and healthy controls, during negative emotion processing using fMRI. **Methods:** Twenty SCZ+V, 19 SCZ-V, and 21 healthy men were scanned while viewing negative images. **Results:** Negative images elicited an increased connectivity between the dorsal anterior cingulate cortex (dACC) and the bilateral rostral prefrontal cortex (rPFC), as well as a decreased functional connectivity between the frontal regions (bilateral rPFC and dACC) and the putamen and hippocampus in SCZ+V men as compared to SCZ-V men and healthy controls. Concurrently, the centrality of the dACC within the network was reduced in SCV+V subjects. **Conclusions:** These results suggest an inefficient integration of the information by the dACC between frontal and limbic regions in SCZ+V men during negative emotion processing and highlight the importance of the ACC in the neurobiological basis of violent behavior in schizophrenia.

**Keywords:** schizophrenia, violence, negative emotions, anterior cingulate cortex, functional connectivity, fMRI

## Introduction

Although individuals with schizophrenia (SCZ) are at an increased risk of presenting violent behaviors compared to the general population (Brennan, Mednick & Hodgins, 2000; Fazel et al., 2009), the current understanding of the neurobiological mechanisms underlying the emergence of such behaviors is limited (Hoptman & Antonius, 2011). A defective processing of negative emotions such as fear and anger in violent individuals has been proposed (Coccaro et al., 2011; Kumari, Das, et al., 2009; Roberton, Daffern & Bucks, 2012), as these negative emotions were shown to precipitate violence and aggression (Chereji, Pintea & David, 2012; Reagu et al., 2013). Considering that the system of structures involved in the experience, processing, and regulation of emotions include the prefrontal cortex, amygdala, hippocampus, insula, striatum, and anterior cingulate cortex (ACC), Davidson, Putnam and Larson (2000) have suggested that dysfunctions within this system might be implicated in the failure to regulate negative emotions and potentially contribute to an increased predisposition for aggressive and violent behaviors. Given the growing association between negative affect and violent behavior in the context of psychotic disorders (Coid et al., 2016; Reagu et al., 2013; Ullrich, Keers & Coid, 2014), similar abnormalities might be expected in violent men with (SCZ+V) or without schizophrenia (Joyal et al., 2007; Naudts & Hodgins, 2006; Stahl, 2014).

Structural alterations within the emotional-salience network of violent SCZ patients have generally supported this assumption (Fjellvang, Grøning & Haukvik, 2018; Leclerc et al., 2018; Widmayer et al., 2018). Reduced brain volumes in the hippocampus (Barkataki et al., 2006; Kumari, Barkataki, et al., 2009; Yang et al., 2010), parahippocampus (Yang et al., 2010), amygdala (Wong et al., 1997), ACC (Kumari et al., 2014), orbitofrontal cortex (Kumari, Barkataki, et al., 2009), and cerebellum (Puri et al., 2008), and increased gray matter volumes

in the putamen (Barkataki et al., 2006) have been observed among SCZ+V subjects. Increased gray matter volumes in the hypothalamus and right precuneus in SCZ men with a history of conduct disorder (Schiffer et al., 2013), and larger orbitofrontal cortex (Hoptman et al., 2005) and caudate volumes (Hoptman et al., 2006) amongst SCZ men with high levels of aggressive behavior have also been reported. However, these structural differences do not provide an insight into the alterations involved in the processing of stimuli that may trigger violent behavior.

Few functional neuroimaging studies have examined emotion processing among men with SCZ in relation to violence/aggression or traits related to them (Fjellvang et al., 2018; Soyka, 2011). Dolan and Fullam (2009) observed blunted amygdala response to fearful faces in SCZ men with high levels of psychopathic traits in comparison to SCZ men with low psychopathic traits. Kumari, Das, et al. (2009) reported greater activity in the thalamus and the caudate nucleus in response to threat stimuli in SCZ+V men relative to non-psychotic individuals diagnosed with antisocial personality disorder. Recent work by our laboratory has found a hyperactivated ventral ACC during the processing of negative emotion (Tikasz et al., 2016), and a deficit in dorsolateral prefrontal cortex activation when inhibiting a response while viewing angry faces (Tikasz et al., 2017) in schizophrenia individuals with a history of violent/aggressive behavior relative to both non-violent SCZ (SCZ-V) and healthy subjects. These results suggest abnormalities in the emotional-salience network that encompass regions involved in emotion regulation (Davidson et al., 2000) among men with SCZ+V during the processing of negative emotions.

Hoptman et al. (2009) have authored the sole study to date to investigate functional connectivity in relation with violent/aggression among SCZ subjects. They reported reduced

functional connectivity at rest between the amygdala and ventral prefrontal regions in male schizophrenia patients, which correlated inversely with aggression. These results, although concordant with current conceptualizations of the neurobiological basis of violence implying a disrupted fronto-limbic network (Coccaro et al., 2011; Leclerc et al., 2018; Rosell & Siever, 2015; Soyka, 2011; Stahl, 2014), do not allow to infer deficits specific to distinct cognitive/emotional states that have been associated with the emergence of violence in SCZ, such as negative emotion processing and regulation (Davidson et al., 2000; Reagu et al., 2013; Roberton et al., 2012). Moreover, their results were based on the analysis of single pairs of regions, although the neurobiology of violence is likely to involve a larger set of brain regions from the emotion salience network. Nevertheless, the seminal work of Hoptman et al. (2009), as well as previous work in functional and structural imaging in SCZ+V, are an incentive to investigate broader functional connectivity disruptions within the emotional-salience network during the processing of negative emotions in a population of SCZ with a reported history of serious violence.

Currently, the understanding of the neural underpinning of emotion processing in SCZ+V is limited. Therefore, using adequate control groups, this study sought to identify disrupted functional connectivity within the emotional-salience network among men with SCZ+V, compared to men with SCZ-V and healthy controls, during negative emotion processing. We hypothesized that fronto-limbic functional connectivity will be reduced in SCZ+V men compared to the two other groups.

## Methods

*Participants*

A total of 60 male participants were recruited for this study. Based on the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) criteria, thirty-nine outpatients with schizophrenia (SCZ) or schizo-affective disorder were included. Nineteen patients without (SCZ-V) and 20 patients with (SCZ+V) a history of serious violent behavior were recruited from general and forensic psychiatric hospitals, respectively. Serious violence was defined as "a history of armed aggression resulting in injuries or death" (Tikasz et al., 2016) and was assessed based on the *Structured Clinical Interview for DSM-IV* (SCID-IV) (Spitzer et al., 1992), the *MacArthur Community Violence Instrument* (Monahan et al., 2001), and clinical files. The number of DSM-IV diagnostic criteria for antisocial personality disorder met by participants with a history of violence were calculated. All patients were stabilized on antipsychotic medication (no changes for >2 months) prior to participating in the study. Antipsychotic dosage was compared between patients using chlorpromazine equivalents (Woods, 2003). Symptom severity was evaluated with the *Positive And Negative Syndrome Scale* (Kay, Fiszbein & Opler, 1987) yielding five sub-scores: positive, negative, disorganization/cognitive, excitation, and depression (Lindenmayer, Grochowski & Hyman, 1995). Urine drug screenings were administered. Twenty-one healthy men with no history of violent behavior or mental disorders were recruited. Healthy participants were screened with the non-patient edition of the SCID-IV (Spitzer et al., 1992). Participants were free of concomitant neurological disorders, substance use disorders (lifetime for Healthy subjects; last 12 months for SCZ), or magnetic resonance imaging (MRI) contraindications. Participants had an IQ > 70 (Wechsler, 2011). Parental socioeconomic status (SES) was assessed according to the National

Occupational Classification (Human Resources and Skills Development Canada, 2001). Informed consent was obtained from all individual participants included in the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee from the *Regroupement de Neuroimagerie du Québec*, the *Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal*, and the *Institut Philippe-Pinel de Montréal*. All subjects gave written informed consent in accordance with the 1964 Declaration of Helsinki.

*Experimental procedure and task*

While in the scanner, participants were shown blocks of emotional pictures taken from the *International Affective Picture System* (IAPS) (Lang, Bradley & Cuthbert, 2008). Based on IAPS normative data, the pictures were grouped by valence (i.e., negative, positive, neutral) and arousal intensity (i.e., high arousal, low arousal), yielding 5 conditions: *i)* high arousal positive, *ii)* high arousal negative, *iii)* low arousal positive, *iv)* low arousal negative, and *v)* neutral. Each condition was presented in two separate 48.5 s blocks, except for the neutral block which was presented four times. Each block contained 10 images from the same condition, each image appearing for 3 s followed by a fixation point presented on a blank screen for 1.75 s (ITI: 4.75 s). Blocks were interceded by 16 s rest periods, and the order of the blocks was pseudo-randomized. Preceding each block was a 3 s period when participants were instructed on screen to press a button whenever they saw a person in the picture. This measure was to ensure participants were attentive to the content of the images they were presented. The task was explained in detail to the participants prior to undergoing the experiment, and they received no additional training outside of the scanner.

Following the fMRI session, participants rated the images from 0 to 8, corresponding to an absence of any emotional reaction to the strongest emotion ever felt, respectively.

*MRI Data Acquisition Parameters*

All images were acquired on a 3.0 Tesla TRIO-TIM system. Blood oxygen level dependent (BOLD) signal was recorded using a T2-weighted gradient echo-planar imaging (EPI) sequence with an inline retrospective motion correction algorithm. Forty-one axial slices angled parallel to the AC-PC line were acquired (TR: 3,000ms), with 3.5mm isotropic voxels, yielding a 64 × 46 matrix. Using a 3D spoiled gradient echo sequence, 176 co-planar sagittal anatomical slices with 1mm isotropic voxels were also acquired, yielding a 256 × 256 matrix.

*fMRI Data Preprocessing*

fMRI data was analyzed with the CONN v.17 functional connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The default preprocessing pipeline was utilized, constituted of SPM v.12 functions (Ashburner et al., 2014). Functional images were realigned, centered, slice-time corrected, corrected for motion artifacts with the Artifact Detection Toolbox (Whitfield-Gabrieli, Nieto-Castanon & Ghosh, 2011), and co-registered to the corresponding anatomical image. The anatomical images were centered, segmented (into gray matter, white matter, and cerebrospinal fluid) and normalized to the *Montreal Neurological Institute* (MNI) stereotaxic space. Functional images were normalized to MNI stereotaxic space using the deformation field from the corresponding anatomical images, spatially smoothed with a 3D isotropic Gaussian kernel (8mm FWHM), and resliced to 2 $mm^3$ voxels.

*Functional connectivity analysis*

A seed-driven approach was employed for functional connectivity analyses (Behzadi et al., 2007). The anatomical component-based noise correction method was used to estimate the physiological BOLD signal noise from the white matter and cerebrospinal fluid (Behzadi et al., 2007). These physiological noise processes, together with the 6 realignment parameters and the scans impacted by movement artifacts (scrubbing) were regressed out as first-level nuisance covariates from the BOLD time-series at each voxel. The main activation effects of the conditions were also accounted for to avoid spurious connectivity due to task co-activation (Sheldon et al., 2016). Linear detrending was performed. The time-series were band-pass filtered (0.008–0.090Hz), and then weighted by the appropriate HRF-convolved regressor to derive task condition-specific timeseries for weighted functional connectivity analyses (Sandberg, Bohland & Kiran, 2015; Whitfield-Gabrieli & Nieto-Castanon, 2012). We limited our primary investigations to the processing of negative pictures (high & low arousal together) based on previous results from our research team (Tikasz et al., 2016), which showed the processing of negative emotions to be the most altered in SCZ+V men. Secondary analyses were performed using the positive emotion and neutral conditions.

The 10 seeds/regions of interest (ROIs) were chosen from the Harvard-Oxford atlas. The bilateral rostral prefrontal cortex (rPFC), dorsal ACC (dACC), ventral ACC (vACC), bilateral hippocampus, bilateral putamen, and bilateral amygdala (Table 1) were included based on studies in non-psychotic and SCZ populations that have suggested these regions to be implicated in the neurobiology of violence and aggression (Davidson et al., 2000; Hoptman et al., 2009; Rosell & Siever, 2015) including results from our laboratory (Tikasz et al., 2017).

Table 1. Regions-of-interest used as seed in functional connectivity analysis

| Seed | l/r | MNI coordinates | | |
|---|---|---|---|---|
| | | x | y | z |
| Dorsal Anterior Cingulate Cortex (dACC) | - | 0 | 22 | 35 |
| Ventral Anterior Cingulate Cortex (vACC) | - | 0 | 21 | -15 |
| Amygdala | r | 23 | -4 | -18 |
| Amygdala | l | -23 | -5 | -18 |
| Hippocampus | r | 26 | -21 | -14 |
| Hippocampus | l | -25 | -23 | -14 |
| Putamen | r | 25 | 2 | 0 |
| Putamen | l | -25 | 0 | 0 |
| Rostral Prefrontal Cortex (rPFC) | r | 32 | 46 | 27 |
| Rostral Prefrontal Cortex (rPFC) | l | -32 | 45 | 27 |

*l, left; r, right.*

In the first-level correlation maps, Pearson's correlation coefficients were calculated between the time-course of each pair of ROIs for each subject. Resulting correlation coefficients were converted to normally distributed Z-scores using Fisher's transform to improve second-level General Linear Model analyses (Whitfield-Gabrieli & Nieto-Castanon, 2012). Second-level analysis compared the correlation coefficients between groups using the group contrast vector c = [−0.5 −0.5 1] to search for connections that were altered in SCZ+V [1] subjects in comparison to both SCZ-V [−0.5] and Healthy subjects [−0.5].

Second-level analyses were corrected for multiple comparison using a $p$-FDR < 0.05 threshold applied at the analysis-level. This is a conservative correction which considers the total number of individual connections in the entire analysis (10 ROIs yielding 45 individual connections) and allows for the identification of between-group differences in the strength of individual connections. To confirm that the effects were specific to SCZ+V subjects, post-hoc tests were computed for all possible pair-wise comparisons. GIMP was used to build the figures (www.gimp.org).

*Network Analysis*

Network analysis was employed to quantitively characterize the between-group differences in topological organization of the functional connectome (Wang, Zuo & He, 2010) during the processing of negative emotions. Analyses were done with the GRETNA toolbox (Wang et al., 2015). The absolute values of the coefficients from the Fisher-Z transformed correlation matrices extracted from CONN were considered, and diagonal entries were set to zero. A cost threshold range of 0.10-0.34 (i.e., 10% to 34% of the strongest possible connections) with intervals of 0.01 was employed (Lei et al., 2015; Suo et al., 2015; Zhang et al., 2011; Zhu et al., 2016). Analyses were performed using binary undirected graphs, where connections that met the cost-threshold were set to 1 and all other connections were set to 0. The area under the curve for the range of cost-threshold was calculated for each network metric employed, which provided a cost-integrated value (Smucny et al., 2017) for each subject that was independent of a single threshold selection (Lei et al., 2015), and could be used for group analyses.

Based on recent studies in schizophrenia (Smucny et al., 2017) and other populations (Tinaz et al., 2016), commonly used global metrics were examined, including global and local network efficiency, and regional network metrics, including the betweenness-centrality (reflecting how a brain region is used to enable one area to communicate with another), nodal clustering coefficient (reflecting the level of local connectedness of a node), and nodal local efficiency (a measure of local information transfer). Additional details can be found in Rubinov and Sporns (2010).

Cost-integrated metrics were entered in an ANOVA, and *post-hoc* tests were computed for all possible pairwise comparison. Nodes/seeds that showed significant between-group differences in functional connectivity were the focus of the network analysis.

*Clinical data*

Correlation analyses between clinical variables, functional connectivity, and cost-integrated network metrics were calculated. A significance threshold of $p < 0.05$ was implemented.

## Results

*Participant characteristics*

As described in Tikasz et al. (2016), no between-group differences were observed for the participants' age, handedness, and ratings of negative images. Furthermore, SCZ+V participants did not differ from SCZ-V participants with regards to diagnosis, age of onset, illness duration, negative symptoms, chlorpromazine equivalents, and treatment with clozapine. However, SCZ+V subjects reported lower parental SES than Healthy subjects, and SCZ+V subjects presented fewer positive and disorganized symptoms than SCZ-V subjects (Table S1). Participants with a history of violence did not report sexual violence. Of the participants reporting violent behaviors, 8 met the criteria for antisocial personality disorder with evidence of conduct disorder in childhood.

*Functional connectivity analysis*

During negative emotion processing, the SCZ+V group showed distributed alterations in task-modulated functional connectivity (Table 2, Figure 1). In comparison to SCZ-V and Healthy subjects, SCZ+V showed altered patterns of connections at the left and right rPFC, left and right hippocampus, right putamen, and the dACC. Moreover, *post-hoc* analysis revealed that the strength of the individual connections was specifically altered in SCZ+V when compared to

*both* SCZ-V and Healthy subjects. The strength of the connectivity between the left rPFC, the right rPFC and the dACC was *increased* in SCZ+V participants compared to both groups. Conversely, in SCZ+V participants, reduced connections were observed between: *i)* the left rPFC and the bilateral hippocampus, right putamen; *ii)* the right rPFC and the right hippocampus; *iii)* the dACC and the bilateral putamen, right hippocampus. When positive symptoms were considered as covariates, the reduced connectivity between the left rPFC and the left hippocampus was no longer different between groups. Parental SES, disorganization symptoms, chlorpromazine equivalents and clozapine had no influence on the results (all $p > 0.05$). No between-group differences were observed during positive and neutral emotion processing for any of the connections found to be impaired during negative emotion processing. The group mean Fisher's Z-scores can be found in Table S2.

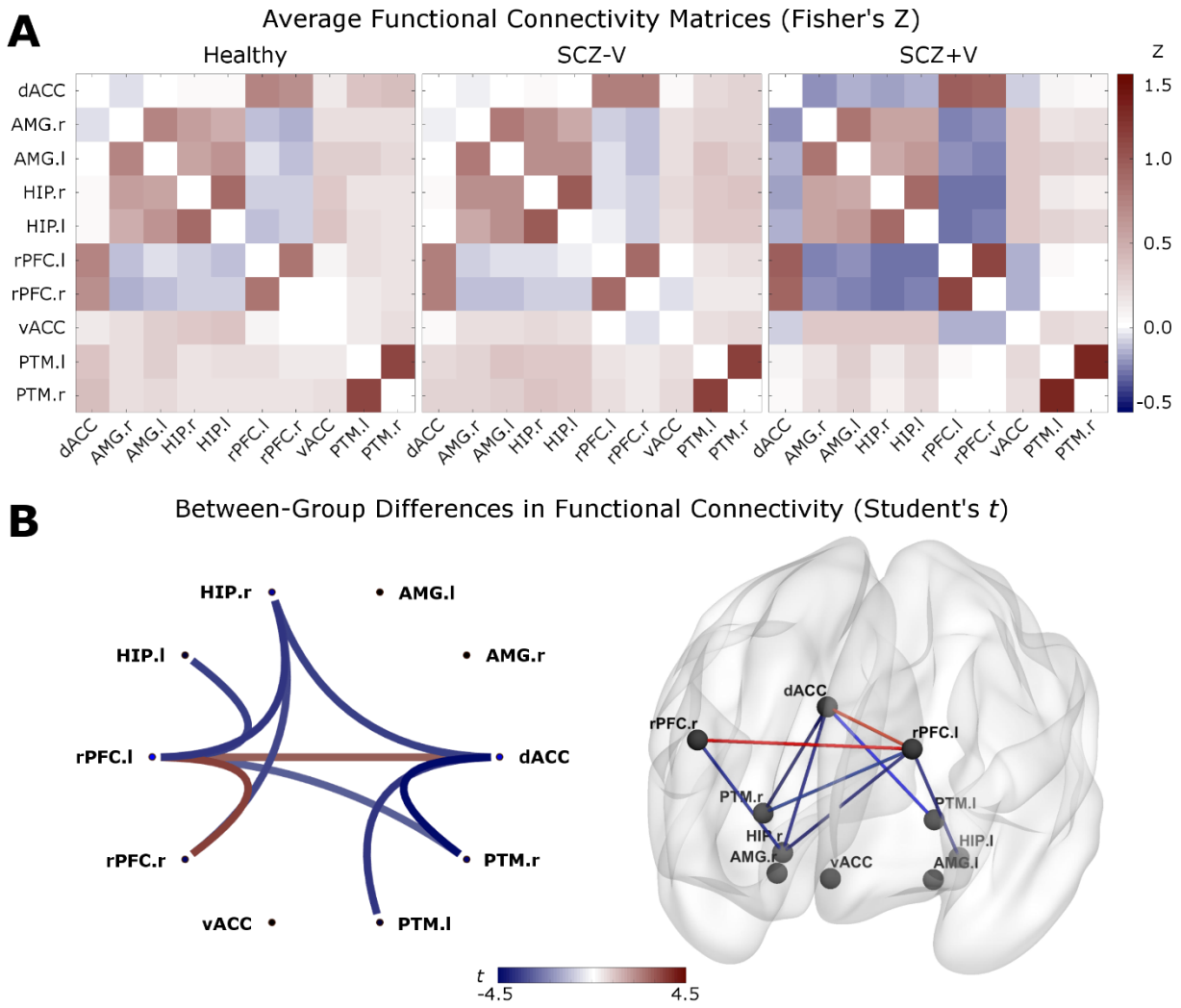


Figure 1. **(A)** Averaged functional connectivity (correlation) matrices (Fisher's Z-score) between each pair of regions for the three groups. The second level analysis was based on these measures. In red: positive correlations; in blue: negative correlations. **(B)** Between-group differences (contrast vector = [−0.5 −0.5 1]) in functional connectivity comparing SCZ+V [1] subjects to SCZ-V [−0.5] and Healthy subjects [−0.5] ($p$-FDR < 0.05 analysis-level). In red: Increased connectivity in SCZ+V subjects, relative to the two other groups; in blue: reduced connectivity in SCZ+V subjects, relative to the two other groups. When positive symptoms were considered as covariates, the reduced connectivity between the left rPFC and the left hippocampus was no longer different between groups. SCZ, schizophrenia; V, violent behavior dACC, dorsal anterior cingulate cortex; vACC, ventral anterior cingulate cortex; rPFC, rostral prefrontal cortex; PTM, putamen; HIP, hippocampus; AMG, amygdala; r, right; l, left.

Table 2. Between-group differences [SCZ+V vs SCZ-V & Healthy] for ROI-to-ROI functional connectivity during negative emotion processing.

| Seed ROI | Target ROI | T* | *Post-Hoc* LSD |
|---|---|---|---|
| Putamen r | | | |
| | dACC | -4.50 | SCZ+V < SCZ-V < Healthy |
| | rPFC l | -2.92 | SCZ+V < SCZ-V & Healthy |
| dACC | | | |
| | Putamen r | -4.50 | SCZ+V < SCZ-V < Healthy |
| | Putamen l | -3.57 | SCZ+V < SCZ-V & Healthy |
| | Hippocampus r | -3.38 | SCZ+V < SCZ-V & Healthy |
| | rPFC l | 2.92 | SCZ+V > SCZ-V & Healthy |
| rPFC l | | | |
| | Hippocampus r | -3.52 | SCZ+V < SCZ-V & Healthy |
| | rPFC r | 3.46 | SCZ+V > SCZ-V & Healthy |
| | Hippocampus l[a] | -3.41 | SCZ+V < SCZ-V & Healthy |
| | dACC | 2.92 | SCZ+V > SCZ-V & Healthy |
| | Putamen r | -2.92 | SCZ+V < SCZ-V & Healthy |
| Putamen l | | | |
| | dACC | -3.57 | SCZ+V < SCZ-V & Healthy |
| rPFC r | | | |
| | rPFC l | 3.46 | SCZ+V > SCZ-V & Healthy |
| | Hippocampus r | -3.28 | SCZ+V < SCZ-V & Healthy |
| Hippocampus l | | | |
| | rRPFC l[a] | -3.41 | SCZ+V < SCZ-V & Healthy |
| Hippocampus r | | | |
| | rPFC l | -3.52 | SCZ+V < SCZ-V & Healthy |
| | dACC | -3.38 | SCZ+V < SCZ-V & Healthy |
| | rPFC r | -3.28 | SCZ+V < SCZ-V & Healthy |

*For all between-group differences in this table, a $p$-FDR < 0.05 analysis-level threshold was applied, which takes into account the total number of connections included in this analysis, and allows to identify between-group differences in the strength of individual connections. Post-hoc Least Significant Difference pairwise test confirmed that SCZ+V men were significantly different from both SCZ-V and Healthy men.

[a]When positive symptoms were considered as covariates, the reduced connectivity between the left rPFC and the left hippocampus was no longer different between groups.

ACC, Anterior cingulate cortex; FDR, False Discovery Rate; LSD, Least Significant Difference; PFC, prefrontal cortex; ROI, region of interest; SCZ, schizophrenia; V, violent behavior.

*Network Analysis*

The network analysis focused on the seeds with significant between-group differences in connection patterns (Table 2). A significant between-group difference was observed in the betweenness-centrality of the dACC ($F = 5.04$, $p = 0.010$; Figure 2). *Post-hoc* ($p < 0.05$) analysis revealed that the metric was decreased in SCZ+V as compared to Healthy subjects. A linear contrast analysis was subsequently conducted, which revealed the betweenness-centrality of the dACC to decrease linearly with group status ($F = 10.04$, $p = 0.002$), where Healthy>SCZ-V>SCZ+V (Figure 2). Between group-difference for betweenness-centrality was also observed for the left rPFC ($F= 4.27$, $p = 0.019$), where *post-hoc* ($p < 0.05$) analysis indicated that the metric was increased in SCZ+V as compared to SCZ-V and Healthy subjects. Furthermore, significant between-group differences were observed for both the nodal clustering coefficient ($F = 6.48$, $p = 0.003$) and the nodal local efficiency ($F = 6.29$, $p= 0.003$) of the dACC. *Post-hoc* ($p < 0.05$) analysis revealed that these two metrics were increased in SCZ+V in comparison to both Healthy and SCZ-V subjects. No between-group differences were observed for the global network metrics (global and local network efficiency). Parental SES, positive and disorganization symptoms, chlorpromazine equivalents and clozapine had no influence on these results (all $p > 0.05$).

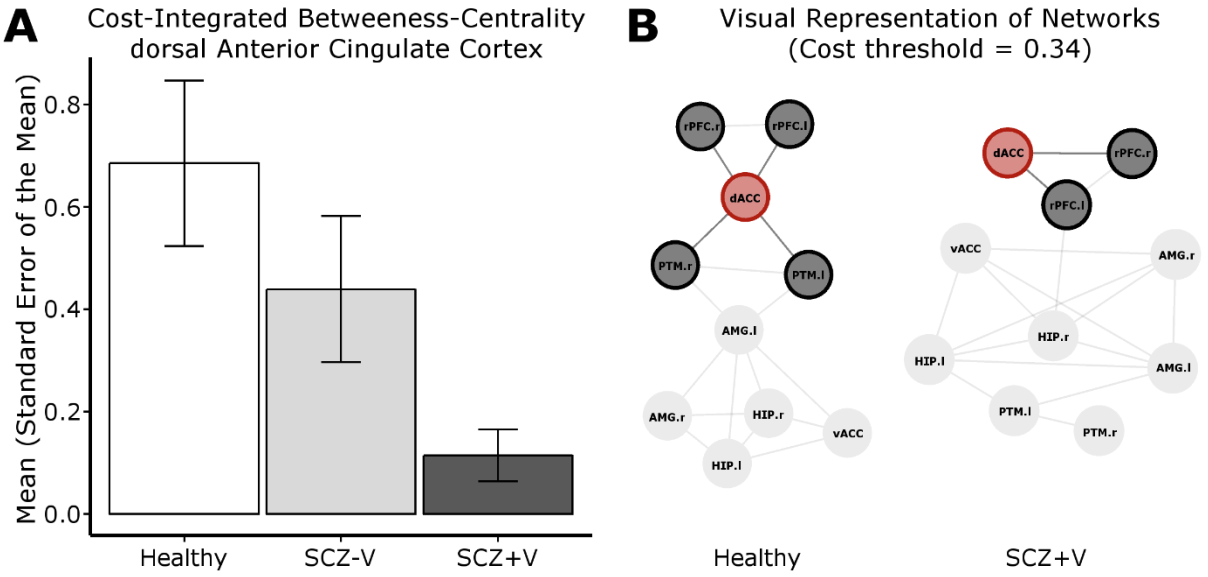


Figure 2. **(A)** Cost integrated betweenness-centrality value for the dACC per group. **(B)** Visual representation of the centrality of the dACC (node in red) within the network of 10 regions investigated. For this representation, Fisher's transformed correlation coefficients were averaged by group, the top 34% coefficients were selected (cost threshold) and binarized. These graphs serve to exemplify that there are more short paths crossing the dACC, therefore holding a higher betweenness-centrality value, in the Healthy subject graph than in the SCZ+V graph. SCZ, schizophrenia; V, violent behavior; dACC, dorsal anterior cingulate cortex; vACC, ventral anterior cingulate cortex; rPFC, rostral prefrontal cortex; PTM, putamen; HIP, hippocampus; AMG, amygdala; r, right; l, left.

*Clinical data*

In Healthy subjects, a positive correlation was observed between the between-centrality value for the dACC and ratings of negative emotional stimuli ($r = 0.542$; $p = 0.017$), as well as between the nodal local efficiency of the dACC and ratings of emotional stimuli ($r = 0.532$; $p = 0.019$). No correlations were observed between functional connectivity or network metrics and subjective ratings or emotional stimuli and antisocial personality traits in SCZ-V and SCZ+V men.

## Discussion

This is the first fMRI study to investigate task-based functional connectivity during the processing of negative emotions in a sample of men with schizophrenia and a history of violence (SCZ+V), as compared to both non-violent men with (SCZV) and without schizophrenia. Viewing negative pictures elicited disrupted functional connectivity in SCZ+V relative to SCZ-V and Healthy subjects in the dACC, bilateral rPFC, right hippocampus and the bilateral putamen. An increased connectivity among SCZ+V men between the dACC and the bilateral rPFC, and concurrently a decreased functional connectivity between the frontal regions (bilateral rPFC and dACC) and the putamen and hippocampus were observed. Furthermore, we observed a gradient effect of group status on the betweenness-centrality of the dACC, as the centrality of the node within the network was reduced in SCZ-V men relative to Healthy subjects, and further reduced in SCZ+V men relative to SCZ-V men. Noteworthy, the connectivity within the emotional salience network during the viewing of positive and neutral pictures did not differ between SCZ+V subjects and the two other groups. Together, these results suggest an inefficient integration of the information by the dACC from frontal and limbic regions in SCZ+V men during negative emotion processing.

The regional betweenness-centrality provides a measure of the capacity of a node to behave as a bridge between the nodes composing the rest of the network, as it is related to the number of shortest paths between two regions passing through. It is a relevant metric within the population investigated, as previous resting-state functional and structural MRI studies have reported a decreased betweenness-centrality (i.e., a less central role within the network) of the ACC in schizophrenia and at-risk populations (Lord et al., 2012; Lord et al., 2011; Smucny et al., 2017; van den Heuvel et al., 2010). In accord with the extant literature in SCZ subjects, we

found a decrease in topological centrality of the dACC in SCZ+V men in comparison to Healthy men. Moreover, we observed a gradient effect between the groups, as the betweenness-centrality of the dACC within the network decreased from Healthy to SCZ-V men, and further decreased from SCZ-V to SCZ+V men. This highlights the compound effect of mental health status (SCZ vs. Healthy) and violence, and shows that the integrative role of the dACC within the emotional salience network is particularly impaired in SCZ+V men.

Concurrently, we observed increased nodal clustering coefficients in SCZ+V men in the dACC. Given that the nodal clustering coefficient is based on the interconnectivity of a node's neighbors (Braun et al., 2012), the increased coefficient is corollary to the aberrant increased connectivity among the dACC, left rPFC, and right rPFC in schizophrenia men with a history of violence. As such, these results are consistent with previous findings of altered dorso-lateral PFC activation in violent schizophrenia subjects during the processing of angry faces (Tikasz et al., 2017). Within the context of emotion processing, the dorso-lateral PFC and dACC are associated with executive control processes (Messina et al., 2016). Interestingly, we found decreased connectivity between the dACC and the right putamen in SCZ-V subjects compared to Healthy participants, and an absence of connectivity in SCZ+V. A decreased/absent coupling could indicate an impairment in communication between systems implicated in cognitive control (conflict and performance monitoring) (dACC) and emotional responding in SCZ+V men. Taken together, these results might suggest compromised negative emotion regulation abilities in SCZ+V men, which is viewed as integral in the adoption of violent behavior (Roberton et al., 2012). Furthermore, we observed a disrupted coupling between frontal regions and the right hippocampus specific to SCZ+V. Meta-analyses of neuroimaging studies have shown that negative emotional stimuli elicit a decreased hippocampal activity in SCZ subjects

compared to healthy controls (Taylor et al., 2012). Taylor et al. (2012) proposed that the hippocampus could be involved in memory retrieval during emotion processing. Therefore, altered coupling between the right hippocampus and the frontal regions could imply a difficulty in contextualizing negative emotions (Fossati, 2012). These results suggest widespread disrupted functional connectivity within the emotional-salience network among SCZ+V men during negative emotion processing, which was posited to be an underlying mechanism in the emergence of aggressive behavior both in schizophrenia and non-psychotic populations (Davidson et al., 2000; Hoptman et al., 2009; Rosell & Siever, 2015). As we did not employ effective connectivity measures, we cannot postulate on the directionality of the impaired connection. That is, we cannot determine if results reflect an aberrant limbic drive and/or a failure of prefrontal executive control mechanisms in the context of negative stimulation (Stahl, 2014). Nevertheless, we observed altered coupling between frontal (rPFC and dACC) and limbic (hippocampus) /striatal (putamen) regions specific to SCZ+V men. These results complement the only study to date in functional connectivity among SCZ men focusing on aggression, which revealed decreased fronto-amygdalar connectivity at rest (Hoptman et al., 2009), and highlight the importance of the dACC in the neurobiology of violent behavior in schizophrenia.

The ACC plays a central role in integrating negative affect and cognitive control through its ventral-affective and dorsal-cognitive subdivisions, respectively (Amodio & Frith, 2006; Bush, Luu & Posner, 2000; Shackman et al., 2011), and is therefore crucial in the neurobiology of violence and aggression (Davidson et al., 2000; Rosell & Siever, 2015). During negative emotion processing in SCZ+V men, we have previously shown a disrupted activity of the ventral ACC indicating an increased neurophysiologic reactivity to emotions (Tikasz et al., 2016), while

in the current study, we found aberrant dorsal ACC functional connectivity patterns consistent with an impaired cognitive control over emotions. The dACC plays a key role in processes that are critical to successful emotion regulation, namely conflict monitoring and performance (error) monitoring (Botvinick, Cohen & Carter, 2004; Etkin, Egner & Kalisch, 2011), as well as emotion awareness (McRae et al., 2008). Taken together, the results from our two studies are complementary and indicate that the ACC plays a crucial role in SCZ+V men that may lead to a difficulty in integrating affective and cognitive aspects of negative emotion processing.

This study presents certain limitations. Both SCZ groups were taking antipsychotic medications which could confound the results, although no between-group differences were observed in chlorpromazine equivalent doses and the number of subjects receiving clozapine (Tikasz et al., 2016). This study also lacked a comparison group of non-psychotic subjects presenting a history of violence. Moreover, psychopathy was not assessed in the present study. Our analyses could have also benefited from a better characterization of the participants' violent behavior, specifically the recency of the behaviors. Furthermore, the IAPS images used in our study were not optimized to investigate discrete emotions, such as anger. Lastly, correlations were utilized as the measure of functional connectivity. Consequently, we cannot infer directionality and/or causality in the connectivity, which limits our capacity to interpret our results as we do not have an indication of brain regions inhibiting or potentiating one another.

**Conclusions**

To conclude, this is the first study to characterize the alterations in functional connectivity and related topological changes of the emotional-salience network during the processing of negative emotion among men with schizophrenia with a history of violence. An increased connectivity

specifically among SCZ+V men between the dACC, left rPFC, and right rPFC, and concurrently, a decrease in functional connectivity between the frontal regions (left/right rPFC and dACC) and the limbic system was observed. These alterations in connectivity translated into a higher regional clustering among the frontal regions, and a decrease in the betweenness-centrality of the dACC within the network. Together with the activation results reported previously by our research team (Tikasz et al., 2016), these results provide a more global picture of the brain functioning alterations during negative emotion processing in SCZ+V men, and highlight the central role of the ACC in the neurobiological bases of violent behavior in schizophrenia. Future studies using effective connectivity are needed to characterize the direction of the connectivity alteration, while paying attention to specific discrete emotions like anger.

## Data Availability Statement

The datasets for this article are not publicly available because the fMRI data were collected with formal approval from the *Regroupement de Neuroimagerie du Québec*, the *Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal*, and the *Institut Philippe-Pinel de Montréal*. They did not approve making anonymized data available. Requests to access the datasets should be directed to AD.

## Ethics Statement

The studies involving human participants were reviewed and approved by the *Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal*, *Regroupement de Neuroimagerie du Québec*, and *Institut Philippe-Pinel de Montréal*. The patients/participants provided their written informed consent to participate in this study.

## Author Contributions

AT wrote the manuscript and did the brain imaging analyses. SP was involved in study design, brain imaging analyses, writing the manuscript, as well as provided critical comments about the manuscript. JD and CF were involved in brain imaging analyses, as well as provided critical comments about the manuscript. VZ and OL were involved in patient recruitment and assessment, as well as provided critical comments about the manuscript. AM was involved in study design, as well as provided critical comments about the manuscript. AD was involved in study design, patient recruitment and assessment, as well as provided critical comments about the manuscript. All authors contributed to and have approved the final manuscript.

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**Supplementary Material**

The Supplementary Material for this article can be found online at:

https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00143/full#supplementary-material

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**Supplementary Material**

Table S1. Characteristics of participants.

| | SCZ+V (n=20) | SCZ-V (n=19) | Healthy controls (n=21) | Significance |
|---|---|---|---|---|
| Age in years, mean (SE) | 30.0 (1.6) | 31.4 (1.7) | 30.9 (1.7) | $F$=0.2; $P$=0.842 |
| Parental SES (SE) | 3.4 (0.3) | 2.9 (0.1) | 2.4 (0.2) | ***F*=4.4; *P*=0.017*** |
| Handedness, % right | 90 | 78.9 | 85.7 | $\chi^2$=4.0; $P$=0.400 |
| Diagnoses | 6 SA | 3 SA | – | $\chi^2$=1.1; $P$=0.292 |
| Age of onset in years (SE) | 21.0 (1.1) | 20.8 (0.8) | – | $F$=0.01; $P$=0.909 |
| Duration of illness (SE) | 9.5 (4.8) | 10.6 (7.5) | – | $F$=0.3; $P$=0.609 |
| PANSS | | | | |
| Positive (SE) | 9.1 (2.4) | 12.1 (0.8) | – | ***F*=9.6; *P*=0.010** |
| Negative (SE) | 12.9 (5.5) | 15.5 (1.3) | – | $F$=2.0; $P$=0.166 |
| Disorganization (SE) | 6.8 (1.9) | 8.5 (0.4) | – | ***F*=7.4; *P*=0.010** |
| Excitation (SE) | 8.3 (3.0) | 7.5 (0.6) | – | $F$=0.6; $P$=0.433 |
| Depression (SE) | 6.5 (2.3) | 7.1 (0.4) | – | $F$=0.7; $P$=0.416 |
| Ratings | | | | |
| Positive images (SE) | 4.6 (0.3) | 4.8 (0.3) | 4.4 (0.3) | $F$=0.3; $P$=0.784 |
| Negative images (SE) | 5.3 (0.4) | 5.3 (0.3) | 5.1 (0.3) | $F$=0.5; $P$=0.603 |
| Neutral images (SE) | 2.4 (0.4) | 2.1 (0.5) | 1.2 (0.3) | ***F*=2.8; *P*=0.072*** |
| Chlorpromazine equivalents in mg (SE) | 846.9 (170.7) | 654.4 (74.7) | – | $F$=1.1; $P$=0.309 |
| Clozapine (n) | 6 | 9 | – | $\chi^2$=1.2; $P$=0.265 |

Significant results are shown in bold (P<0.05). *SCZ−V > Controls ($P$<0.05).
Abbreviations: PANSS, Positive and Negative Syndrome Scale; SA, schizoaffective disorder; SCZ+V, schizophrenia with violent behavior; SCZ−V, schizophrenia without violent behavior; SE, standard error; SES, socioeconomic status (a higher number indicates a lower SES).

Table taken from:

Tikasz, A., Potvin, S., Lungu, O., Joyal, C. C., Hodgins, S., Mendrek, A., & Dumais, A. (2016). Anterior cingulate hyperactivations during negative emotion processing among men with schizophrenia and a history of violent behavior. *Neuropsychiatric Disease and Treatment, 12*, 1397-1410.

Table S2. Group mean Fisher's Z-score (Standard Error of the Mean) for ROI-to-ROI functional connectivity during negative emotion processing.

| Seed ROI | Target ROI | Healthy | | SCZ-V | | SCZ+V | |
|---|---|---|---|---|---|---|---|
| Putamen r | | | | | | | |
| | dACC | 0.376 | (0.178) | 0.254 | (0.241) | 0.055 | (0.213) |
| | rPFC l | 0.186 | (0.187) | 0.193 | (0.194) | 0.029 | (0.219) |
| dACC | | | | | | | |
| | Putamen r | 0.376 | (0.178) | 0.254 | (0.241) | 0.055 | (0.213) |
| | Putamen l | 0.353 | (0.191) | 0.230 | (0.237) | 0.078 | (0.226) |
| | Hippocampus r | 0.044 | (0.145) | 0.045 | (0.341) | -0.184 | (0.225) |
| | rPFC l | 0.730 | (0.194) | 0.775 | (0.256) | 0.957 | (0.307) |
| rPFC l | | | | | | | |
| | Hippocampus r | -0.082 | (0.175) | -0.049 | (0.264) | -0.266 | (0.177) |
| | rPFC r | 0.820 | (0.245) | 0.877 | (0.295) | 1.123 | (0.325) |
| | Hippocampus l | -0.097 | (0.178) | -0.015 | (0.235) | -0.250 | (0.210) |
| | dACC | 0.730 | (0.194) | 0.775 | (0.256) | 0.957 | (0.307) |
| | Putamen r | 0.186 | (0.187) | 0.193 | (0.194) | 0.029 | (0.219) |
| Putamen l | | | | | | | |
| | dACC | 0.353 | (0.191) | 0.230 | (0.237) | 0.078 | (0.226) |
| rPFC r | | | | | | | |
| | rPFC l | 0.820 | (0.245) | 0.877 | (0.295) | 1.123 | (0.325) |
| | Hippocampus r | -0.070 | (0.128) | -0.071 | (0.258) | -0.254 | (0.213) |
| Hippocampus l | | | | | | | |
| | rRPFC l | -0.097 | (0.178) | -0.015 | (0.235) | -0.250 | (0.210) |
| Hippocampus r | | | | | | | |
| | rPFC l | -0.082 | (0.175) | -0.049 | (0.264) | -0.266 | (0.177) |
| | dACC | 0.044 | (0.145) | 0.045 | (0.341) | -0.184 | (0.225) |
| | rPFC r | -0.070 | (0.128) | -0.071 | (0.258) | -0.254 | (0.213) |

Abbreviations: ACC, Anterior cingulate cortex; PFC, prefrontal cortex; ROI, region of interest; r, right; l, left.

# 4 Reduced dorsolateral prefrontal cortex activation during affective Go/NoGo in violent schizophrenia patients: An fMRI study

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**Abstract**

We investigated the influence of anger processing on cognitive control in male schizophrenia patients presenting violent behaviors. We recruited 23 patients without and 24 patients with (SCZ+V) a history of violent behaviors, as well as 22 healthy non-violent men. Participants were administered an affective (angry-neutral faces) Go/ NoGo task while undergoing functional magnetic resonance imaging. We found a reduced activation in the dorsolateral prefrontal cortex in SCZ+V patients specifically when inhibiting a response while viewing angry faces. These results show deficits in the (inhibitory) cognitive control network of SCZ+V in the context of anger.

**Keywords:** schizophrenia, violence, anger, cognitive control, Go/NoGo, fMRI

## Introduction

Despite a 2.1 to 4.6 times increase in the risk of violent behavior among people with schizophrenia compared to the general population (Brennan, Mednick & Hodgins, 2000; Fazel et al., 2009), the neurobiological mechanisms involved in the emergence of violent behaviors are seldom investigated, and consequently not well understood (Hoptman & Antonius, 2011). Among non-psychotic individuals, dysfunctional regulation of negative emotions, especially anger and impulsivity, have been proposed as important risk factors in the emergence of violent behaviors (Davidson, Putnam & Larson, 2000). Neuroimaging studies investigating anger processing (i.e., emotion processing) and impulsivity (e.g., cognitive control) in violent non-psychotic individuals have shown deficits in limbic (amygdala and anterior cingulate cortex (ACC)) and executive (dorsolateral prefrontal cortex (DLPFC), and inferior frontal gyrus) systems, respectively (Davidson et al., 2000). Conversely, there have only been few attempts at investigating dysregulations in schizophrenia pertaining to the processing/regulation of negative emotions and impulsivity, especially cognitive control (Joyal et al., 2007; Tikasz et al., 2016), yet results indicate anomalies concordant with those observed in violent non-psychotic individuals. In fact, Hoptman et al. (2014) observed negative urgency, a measure incorporating negative affect with impulsivity, to be associated with reduced functional connectivity between executive and limbic regions among schizophrenia patients.

It has been hypothesized that violent behavior exhibited by persons with schizophrenia stems from a difficulty to self-regulate, which occurs when anger is elevated (Reagu et al., 2013). Yet, the interactions between the systems underlying cognitive control and emotion processing have not been investigated among persons with schizophrenia displaying violent behaviors. This is even more peculiar when considering that the executive system was shown to

be less efficient during the experience of negative emotions, such as anger (Brown et al., 2012). The current study was conducted to test the hypothesis that dysregulation of the executive system, especially in the presence of anger, would distinguish men with schizophrenia who have a history of violence from those who do not.

**Methods**

Forty-seven male patients with schizophrenia (Diagnostic and Statistical Manual of Mental Disorders-IV criteria; 10 inpatients and 37 outpatients; age 18–57 years) were recruited for this study: 23 patients without (SCZ − V) and 24 with a history of violence (SCZ+V). Examples of violent behaviors reported were attempted and/or completed homicide, stabbing, punching, and shooting. Twenty-two healthy men with no history of mental disorders or violence were also recruited. Participants had no concomitant neurological disorders, substance use disorders, or magnetic resonance imaging (MRI) contra-indications. Furthermore, participants had an estimated intelligence quotient (IQ) over 70, as evaluated by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011). Impulsivity was evaluated with the Barratt Impulsivity Scale (BIS) (Patton, Stanford & Barratt, 1995). Symptom severity in patients was evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein & Opler, 1987). The influence of antipsychotics in patients was examined by calculating olanzapine equivalents (Leucht et al., 2014). After a discussion of the study and its implications, all participants gave written consent in accordance with the Declaration of Helsinki. The study was approved by the local ethics committees.

During the functional MRI (fMRI), participants completed an affective Go/NoGo task, during which they viewed 16 static Ekman faces of 4 women and 4 men displaying anger

(Angry) or no emotions (Neutral) (Ekman & Friesen, 1976). The task was divided in two runs, each containing 6 blocks. At the beginning of each block, there was a 20 s rest period followed by a 5 s instruction period specifying the target stimuli requiring a button press (e.g., "Press for women only", where the target gender (Go) = females, and consequently non-target gender (NoGo) = males). The order of the target gender, which alternated between blocks, was randomized between participants. Each block lasted 62 s, and comprised 24 trials (i.e., faces) that were presented in a pseudo- randomized order, where two identical faces were not presented consecutively. Faces were presented for 500 ms, and participants were instructed to respond in that period. Trials were interleaved with fixation crosses presented for either 700, 900, 1100 or 1300 ms. The duration of the fixation cross was randomized, to prevent habituation. Overall, 75% of the stimuli presented were Go stimuli, and 25% stimuli were NoGo stimuli. Furthermore, 50% of the faces viewed were Angry, and 50% were Neutral.

Whole-brain fMRI acquisition was performed using an echo-planar imaging sequence measuring blood oxygenation level dependent (BOLD) signal (TR = 2090 ms; TE = 30 ms; FA = 90°; matrix = 64 × 64; voxel size = 3.5 $mm^3$; 38 axial slices) on a 3 Tesla Siemens Trio MRI system. Individual high-resolution coplanar anatomical images were also acquired during the same scanning session (three-dimensional, ultrafast gradient echo sequence; TR = 2300 ms, TE = 2.98ms; FA = 9°; matrix size = 256 × 240; voxel size = 1 $mm^3$; 176 sagittal slices).

fMRI data were analyzed with BrainVoyager QX 2.8 (Brain Innovation, Maastricht, Netherlands) software. Functional images were slice-time corrected, corrected for motion artifacts (≤2 mm), high-pass filtered (2 cycles per run), co-registered to the corresponding anatomical image, then spatially normalized to the stereotaxic Talairach space, and spatially smoothed with a 3D isotropic Gaussian kernel (8 mm FWHM).

We used a general linear model to identify the cerebral changes associated with response inhibition. Using an event related approach, six predictors of interest (successful Angry-Go, Angry-NoGo, Neutral-Go, Neutral-NoGo, an error predictor (including both commission and inhibition errors), and a predictor for the instructions) were defined and then convolved with the BOLD response estimated using the double gamma model. Only successful trials (inhibition or response) were considered in the fMRI analyses. We undertook a first-level analysis to investigate individual brain-activation maps associated with our primary contrast of interest [Angry-NoGo > Neutral-NoGo]. A second level random-effects model was then computed to investigate between-group differences in activations during response inhibition in the presence of angry faces.

The statistical threshold for significance was determined by Monte Carlo simulation. Assuming a voxel-level threshold of $p < 0.001$ (10,000 simulations), a minimum cluster size of 343mm$^3$ was required to correct for multiple comparisons at $p < 0.05$, brain-wise. The clusters found to significantly differ between the two groups with schizophrenia (SCZ+V vs SCZ−V) were used as data-driven regions of interest (ROI) for subsequent statistical analyses, comparing men with schizophrenia to healthy men. Correlation analyses between regional BOLD responses, task performance, and clinical variables were calculated.

**Results**

Men with schizophrenia (SCZ+V & SCZ−V) had lower IQ, higher levels of impulsivity (BIS total score), and committed more commission errors (i.e., NoGo errors) than healthy men. We observed no differences in age, handedness, and ethnicity between the three groups. The two

groups with schizophrenia did not differ in terms of psychotic symptoms (PANSS), impulsivity (BIS), and medication (see Table 1).

Table 1. Participant characteristics.

| | SCZ+V (n=24) | SCZ-V (n=23) | Healthy (n=22) | Significance |
|---|---|---|---|---|
| Age, mean (SE) | 36.0 (2.1) | 32.8 (1.8) | 31.9 (1.8) | $F$=1.31; $p$=0.28 |
| Handedness, % right | 85.7 | 94.1 | 95.5 | $\chi^2$=3.88; $p$=0.42 |
| Ethnicity, % Caucasian | 75.0 | 87.0 | 86.4 | $\chi^2$=5.19; $p$=0.74 |
| IQ, (SE) | 89.5 (2.9) | 88.9 (2.0) | 100.2 (3.6) | ***F*=4.85; *p*=0.01*** |
| Commission error, % (SE) | 13.0 (2.0) | 12.5 (2.3) | 6.1 (0.9) | ***F*=4.11; *p*=0.02**** |
| Omission error, % (SE) | 26.6 (4.3) | 26.9 (4.4) | 15.9 (2.6) | $F$=2.50; $p$=0.09 |
| BIS Total, (SE) | 63.9 (1.8) | 65.0 (2.1) | 53.6 (1.8) | ***F*=11.27; *p*<0.001**** |
| Diagnoses | 8 SA, 1 SZP | 4 SA | − | $\chi^2$=2.52; $p$=0.28 |
| Age of onset, (SE) | 23.4 (1.9) | 21.3 (1.1) | − | $t$=-1.10; $p$=0.30 |
| PANSS | | | | |
| Positive | 15.5 (0.7) | 16.2 (0.5) | − | $t$=0.78; $p$=0.44 |
| Negative | 17.7 (1.0) | 17.7 (1.2) | − | $t$=0.00; $p$=1.00 |
| General | 36.3 (1.0) | 36.7 (1.4) | − | $t$=0.27; $p$=0.79 |
| Clozapine, % | 39.1 | 50.0 | − | $\chi^2$=0.54; $p$=0.46 |
| Olanzapine equivalents mg, (SE) | 15.5 (2.0) | 13.7 (1.7) | − | $t$=-0.684; $p$=0.50 |

BIS = Barratt Impulsiveness Scale; PANSS = Positive and Negative Syndrome Scale; IQ = Intelligence quotient; SA= Schizo-affective disorder; SZP= Schizophreniform; SCZ+V = schizophrenia with violent behavior; SCZ − V = schizophrenia without violent behavior; SE= standard error of the mean. Bold font indicates significant between-group differences.

* SCZ − V & SCZ+V b Healthy ($p < 0.05$).

** SCZ − V & SCZ+V N Healthy ($p < 0.05$).

For the [Angry-NoGo > Neutral-NoGo] contrast, SCZ+V showed significantly ($p$ < 0.001) decreased activations in the right DLPFC (Talairach coordinates: 36,23,46; Brodmann area 8; cluster size: 514mm$^3$) relative to SCZ-V patients (Fig. 1A). Subsequent ROI analysis of the activation pattern in the DLPFC cluster revealed decreased activation in SCZ+V relative to healthy men ($t$ = 2.335, $p$ = 0.015) (Fig. 1B). Covariance analyses indicated that IQ, impulsivity and commission errors did not influence the main result. Furthermore, the individual parameter estimates of the DLPFC did not correlate with psychotic symptoms, antipsychotic medication, commission errors, or impulsivity among the men with schizophrenia. Using the same ROI, the between-group ANOVA for the [Angry-Go > Neutral-Go] contrast showed a trend level interaction between group and stimuli for the 3 groups ($F_{2,66}$ = 2.978, $p$ = 0.058) (see Fig. S1).

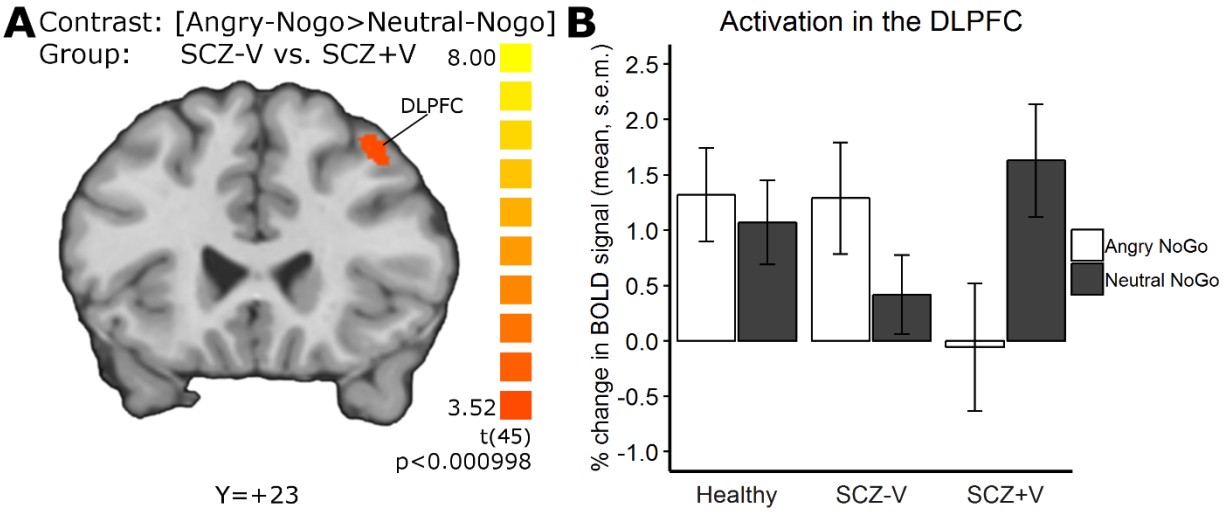


Figure 1. Group differences in BOLD responses of the right dorsolateral prefrontal cortex during response inhibition in the presence of angry faces

**Discussion**

To our knowledge, this is the first fMRI study to investigate the neural mechanisms involved in the interaction between cognitive control and anger processing among violent men with schizophrenia. As predicted, violent men with schizophrenia showed a hypoactivation of the DLPFC during a response inhibition task, and the hypoactivation was only present when SCZ+V patients had to process angry faces. The DLPFC is a core region of the executive system, playing a key role in cognitive control (Criaud & Boulinguez, 2013). These results are consistent with recent evidence indicating that DLPFC activity during cognitive control is influenced by the emotional context (Cromheeke & Mueller, 2014).

Our finding suggests a neurobiological mechanism contributing to violent behaviors among men with schizophrenia, as it strikingly echoes the fact that such men are characterized by difficulty in self-regulation, especially when they are angry (Reagu et al., 2013). Our results suggest that this difficulty may be related to an inability to recruit a core region of the (inhibitory) cognitive control network (e.g., DLPFC) specifically in the context of anger. Krakowski et al. (2016) have described similar results in violent schizophrenia patients, where strong reactivity to negative stimuli in those patients interfered with response inhibition as manifested by a reduction of the P3 event-related potential component.

Among the violent men with schizophrenia, we observed a reduced activation of the DLPFC during Angry-NoGo events, and a similar trend was observed during Angry-Go events. This could indicate that the abnormal DLPFC responses of the violent men with schizophrenia are not related to a specific interaction between emotion and cognitive control per se (e.g., NoGo events), but to an interaction between emotion and the attentional aspects of the task (e.g., Go and NoGo events). A strength of the study was the relatively large sample of men with

schizophrenia. Most importantly, this was the first fMRI study in this population that modeled the interaction between affective context and cognitive control. Future studies are needed to compare the effects reported in schizophrenia to violent non-mentally ill individuals to better disentangle the specific influences of violence and psychosis on our observations. Furthermore, studies should include continuous measures of violent/aggressive behavior in order to investigate the effect of the severity and intensity of the behaviors against the neuroimaging data.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.11.011.

**Contributors**

AT wrote the manuscript, was involved with participant testing, and did the brain imaging analyses; SP was involved in study design, writing the manuscript, as well as provided critical comments about the manuscript; SRD was involved in study design as well as provided critical comments about the manuscript; OLipp was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; SH was involved in study design as well as provided critical comments about the manuscript; PL was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; OLungu was involved in the brain imaging analyses, as well as provided critical comments about the manuscript; AD was involved in study design, patient recruitment and assessment, as well as provided critical comments about the manuscript. All authors contributed to and have approved the final manuscript.

**Role of funding source**

The funding sources had no input in the design of the study, data collection, data analysis and interpretation, and in writing the final report.

**Conflict of interest**

AD and SP are co-PIs on a grant from Otsuka Pharmaceuticals; SP is co-investigator on a grant from INSYS Pharmaceuticals. Drs. Potvin, Richard-Devantoy, Lipp, Hodgins, Lalonde, Lungu, and Dumais, as well as M. Tikàsz, reported no biomedical financial interests or potential conflicts of interest.

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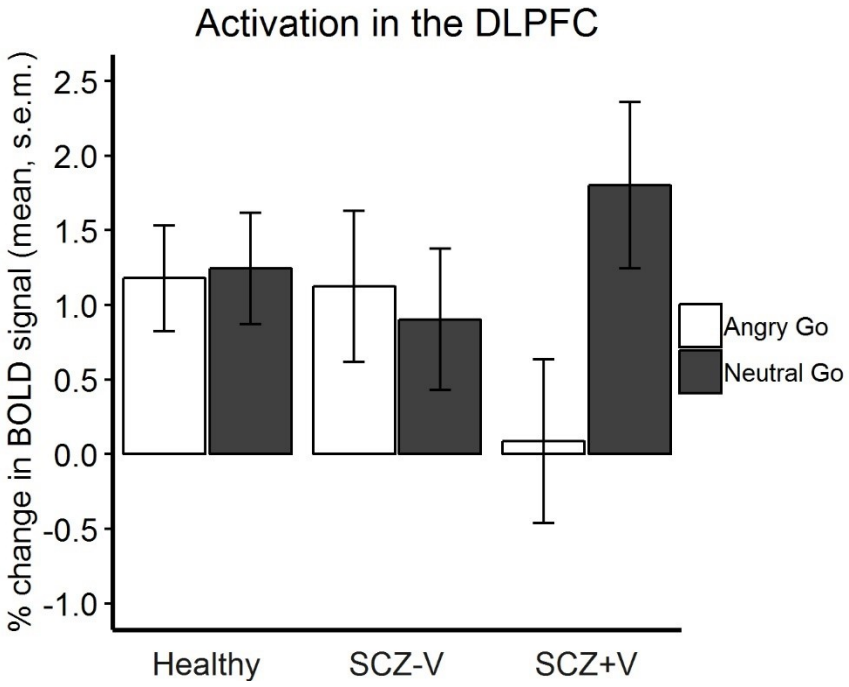
**Supplementary Material**

Figure S1. BOLD signal during Go stimuli in an emotional context



# 5 Reward-related decision-making in schizophrenia: A multimodal neuroimaging study

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**Abstract**

Schizophrenia is a severe psychiatric disorder characterized by important cognitive deficits, which ultimately compromise the patients' ability to make optimal decisions. Unfortunately, the neurobiological bases of impaired reward-related decision-making in schizophrenia have rarely been studied. The objective of this study is to examine the neural mechanisms involved in reward-related decision-making in schizophrenia, using functional magnetic resonance imaging (fMRI). Forty-seven schizophrenia patients (DSM-IV criteria) and 23 healthy subjects with no psychiatric disorders were scanned using fMRI while performing the Balloon Analogue Risk Task (BART). A rapid event-related fMRI paradigm was used, separating decision and outcome events. Between-group differences in gray matter volumes were assessed with voxel-based morphometry. During the reward outcomes, increased activations were observed in schizophrenia in the left anterior insula, the putamen, and frontal subregions. Reduced gray matter volumes were observed in the left anterior insula in schizophrenia which spatially overlapped with functional alterations. Finally, schizophrenia patients made fewer gains on the BART. The fact that schizophrenia patients had increased activations in sub-cortical regions such as the striatum and insula in response to reward events suggests that the impaired decision-making abilities of these patients are mostly driven by an overvaluation of outcome stimuli.

**Keywords:** schizophrenia, decision-making, reward, fMRI, insula, striatum

## Introduction

Schizophrenia is a severe and complex psychiatric disorder associated with poor social and occupational functioning (Green, 1996). The disorder is characterized by significant cognitive and affective impairments (Bora, Yücel & Pantelis, 2010; Habel et al., 2000), which ultimately compromise the patients' ability to make practical decisions. Clinical manifestations of impaired decision-making in schizophrenia are numerous, and include substance misuse (Hartz et al., 2017), occupational and financial problems (Marson, Savage & Phillips, 2006), proneness to pathological gambling (Desai & Potenza, 2009), self-harm (Haddock et al., 2013), as well as interpersonal problems (McGuire, Brüne & Langdon, 2017). Unfortunately, the pathophysiological bases of impaired reward-related decision making in schizophrenia have been rarely studied, and thereby remain poorly understood.

Optimal decision-making requires to adapt choices based on the outcomes (rewards and punishments) of previous choices. Several cognitive studies have examined reward related decision-making in schizophrenia. Recently, Brown et al. (2015) performed a meta-analysis of 8 studies that have addressed this question using the Iowa Gambling Task (IGT) (Bechara et al., 1994), whereby participants need to choose between 4 decks offering small rewards and smaller punishments (i.e., advantageous decks) or large rewards and larger punishments (i.e., disadvantageous decks). The results of the meta-analysis showed that schizophrenia patients have moderate deficits in reward related decision- making as illustrated by an increased selection of disadvantageous decks over advantageous ones. Despite this, a paucity of studies have examined the neurobiological mechanisms involved in suboptimal reward related decision-making in schizophrenia. Preliminary functional neuroimaging studies on reward-related decision-making in this population have highlighted impairments in the ventral striatum (Brown

et al., 2015; Rausch et al., 2014; Richter et al., 2015), a key region of the brain reward system. The neuroanatomical bases of suboptimal reward related decision-making in schizophrenia have also been explored. In a study from Premkumar et al. (2008) overall performance on the IGT was positively correlated with the left orbitofrontal cortex in healthy subjects, but not in schizophrenia patients.

Thus far, the IGT has been the most frequently employed task to assess reward-related decision-making in schizophrenia (Brown et al., 2015). Despite its importance, the task is complex and requires associative learning of the representations of expectancies (Brambilla et al., 2013). Therefore, poor performance on the IGT in schizophrenia patients may be linked to impaired learning or erroneous calculation of expected value rather than impaired reward-related decision-making. Indeed, the difference between schizophrenia patients and controls on the IGT is mostly apparent for the decks with infrequent punishments, which typically require repeated calculations (Brown et al., 2015). This suggests that the IGT may not entirely be adapted to assess reward related decision-making in this population, which is characterized by learning difficulties (Horan et al., 2008). A relevant alternative to assess reward-related decision-making in schizophrenia is the Balloon Analogue Risk Task (BART) (Bogg et al., 2012), in which participants are presented with a balloon and each time they click on a button, the balloon is incrementally inflated and virtual money is added up to a threshold at which point the balloon explodes. For each balloon, participants must choose whether to cash out or to take the risk of potentially earning more money. The BART has excellent psychometric properties and predictive validity for real-life behavior (Lejuez et al., 2002; Rao et al., 2008; White, Lejuez & de Wit, 2008). It is simple, easy to understand, and less dependent on repeated calculations, which are all important features when assessing reward-related decision-making in

schizophrenia. The functional neuroimaging adaptation of the BART allows the investigation of decision and outcome periods separately, as well as the examination of associations between brain responses and objective risk, based on predetermined probabilities of explosions (Bogg et al., 2012).

In recent years, the BART has become one of the most widely used task to study the neurobiological bases of reward-related decision making. Thus far, the several functional magnetic resonance imaging (fMRI) studies performed in the field have shown that the dorso-lateral prefrontal cortex, medial prefrontal cortex, anterior cingulate cortex, insula, and striatum play a key role in reward-related decision-making in healthy volunteers, with prefrontal regions being more closely involved in decision-making, and sub-cortical regions, in reward processing (Forster, Finn & Brown, 2016; Galván et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). In schizophrenia, preliminary studies using the BART have shown that patients make smaller gains on the task, compared to controls (Cheng et al., 2012; Reddy et al., 2014), suggesting that patients make suboptimal decisions characterized by risk avoidance. Unfortunately, no fMRI study has examined the neural bases of impaired reward-related decision-making in schizophrenia using the BART, at least to our knowledge.

The main objective of the current multimodal neuroimaging study is to examine both the neurofunctional and neuroanatomical bases of suboptimal reward-related decision-making in schizophrenia, using the BART. We hypothesized that schizophrenia patients will make smaller gains on the BART, and that their decisions will be characterized by risk avoidance. At the neural level, we expected to observe, in patients, frontal alterations during decision events and alterations in sub-cortical regions (e.g., striatum and insula) during reward outcomes.

## Methods

*Participants*

Forty-seven male outpatients with schizophrenia or schizoaffective disorder (Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria) were recruited at the Institut Universitaire en Santé Mentale de Montréal and the Institut Philippe-Pinel de Montréal. Diagnoses were established with the Structured Clinical Interview for DSM-IV (First & Gibbon, 2004). Schizophrenia patients reported no comorbid substance use disorders within the last 12 months, and were stabilized on antipsychotic medication (i.e., reported no changes in the 2 months preceding the fMRI session). Schizophrenia participants were treated with one or more of the following antipsychotics: aripiprazole (n=5); clozapine (n=20); olanzapine (n=9); quetiapine (n=10); risperidone (n=6); fluphenazine (n=2); loxitane (n=1); paliperidone (n=5); ziprasidone (n=1). The influence of antipsychotics in patients was examined by calculating olanzapine equivalents (Leucht et al., 2014). Twenty-three heathy men were also recruited, who reported no psychiatric disorder (including substance use disorder), and were not treated with centrally-acting medication. Participants in both groups had no concomitant neurological disorders, unstable medical condition, or MRI contra-indications. Furthermore, all participants had an estimated intelligence quotient (IQ) over 70, as evaluated by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011), and tested negative at an urine drug screening administered before the fMRI session.

After a discussion of the study and its implications, all participants gave written consent in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee.

*Clinical assessments*

In schizophrenia patients, psychiatric symptoms were assessed with the Positive And Negative Syndrome Scale (PANSS) (Kay, Fiszbein & Opler, 1987), which yields five subscores (positive, negative, disorganization/cognitive, excitation, depression) according to Lindenmayer, Grochowski and Hyman (1995)'s five factor model of schizophrenia.

*Balloon analogue risk task*

A slightly modified version of the BART described by Bogg et al. (2012) was employed in this study (see Fig. 1). Prior to the fMRI scanning session, participants completed an abbreviated 5 min block on a laptop to familiarize themselves with the task. The instructions given to the participants were to inflate the balloon without having it explode, and to maximize the total amount of cash earned. The participants were informed that the compensation they received for taking part in the study was not changed in function of the BART outcome. For a given balloon trial, 12 successive inflation responses were possible. The probability of explosion over successive inflation responses increased parametrically (see Bogg et al. (2012)). While in the scanner, participants completed two 8 min runs. Each run began and ended with the display of a fixation cross at the center of the screen. The fixation cross at the beginning lasted 60 s, to establish baseline activity. At the beginning of each trial, the screen displayed an image of a balloon, a square decision cue (green=a response is allowed, red=responses are disallowed), the current wager amount, and the total earnings. Participants had no time restrictions to make a decision (i.e., to choose to Inflate the balloon or Cash In the wager by selecting the appropriate button). The inter-stimuli interval was jittered and randomized, lasting 0 to 6 s after each response. During this delay, no feedback was given, to allow for a separate estimation of the

Blood Oxygen Level Dependent (BOLD) response during choice and outcome periods. Following an inflation of the balloon, the outcome could either be a successful inflation (Success) or an explosion (Explosion). If the balloon was inflated, the decision cue turned red (for 1500, 2000, or 2500 ms) after which the decision cue turned green with the image showing an inflated balloon. If the balloon exploded, the participants were presented with an image showing an exploded balloon (500 ms) and then the words "You Lose!" (1000 ms). After a decision to Cash In, the balloon was replaced by the words "You Win!" (for 1000 ms). After a Win or an Explosion, the screen became black (for 2000, 3000, or 4000 ms), and a new trial was presented.

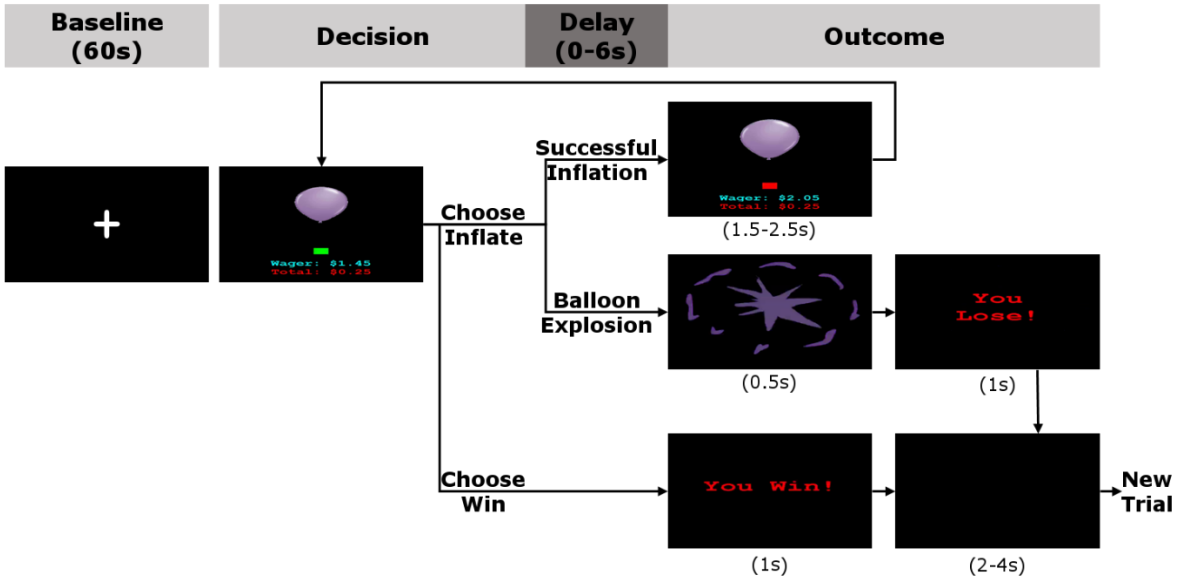


Figure 1. Schematic representation of the modified Balloon Analogue Risk Task (BART) adapted from Bogg et al. (2012).

*MRI data acquisition parameters*

BOLD signal was recorded using a T2-weighted gradient echoplanar imaging (EPI) sequence (TR: 2090 ms; TE: 30 ms; Flip Angle: 90°; matrix: 64×64; voxel size=3.5mm$^3$; 38 axial slices) on a 3.0 Tesla Siemens TRIO MRI system, using a 32-channel, high-resolution, transmit/receive brain volume coil. An inline retrospective motion correction algorithm was employed while the EPI images were acquired. Individual high-resolution co-planar anatomical images were also acquired using a three-dimensional, ultrafast gradient echo sequence (TR: 2300 ms, TE: 2.98 ms, Flip Angle: 9°, matrix: 256×240; voxels size: 1mm$^3$; 176 sagittal slices).

*fMRI data analysis*

fMRI data was analyzed with Brain Voyager QX 2.8 (Brain Innovation, Maastricht, Netherlands) software. Functional images were slice-time corrected, corrected for motion artifacts (≤ 2 mm), high-pass filtered, co-registered to the corresponding anatomical image, spatially normalized to the stereotaxic Talairach space (Talairach & Tournoux, 1988), and spatially smoothed with a 3D isotropic Gaussian kernel (8mm FWHM).

An event-related approach was employed for data analysis. Predictors of interest, corresponding to the experimental events, were convolved with the hemodynamic response function estimated using the double-gamma model. The BART model included five experimental events, namely the decision to Inflate or to Cash In, and the Success, Win and Explosion outcomes. The Explosion event was modelled but was treated as predictor of no interest, due to its low incidence (<5% of outcome events). The predictors were entered as fixed factors in a single-subject general linear model (GLM), and an auto-regressive AR(2) model was used to account for serial correlations. Explosion probabilities (z-transformed) were

included as parametric modulators for the Inflate and Success events (Bogg et al., 2012; Fukunaga, Brown & Bogg, 2012). Then, the parameters of the first-level analysis were entered into a second-level of analysis corresponding to a random-effect GLM that was used for group comparisons (Penny & Holmes, 2007). As in previous fMRI studies, the focus of the group-level analyses were the Inflate and Success events (Bogg et al., 2012; Fukunaga et al., 2012; Schonberg et al., 2012). Knowing that schizophrenia patients tend to attribute motivational value to irrelevant stimuli (Strauss, Waltz & Gold, 2014), the Win event was also considered as an event of interest. As our version of the BART comprised 120 s of baseline activity, we analyzed the events with and without their parametric modulation. The statistical threshold for significance was determined by computing a Monte Carlo simulation (Ward, 2000). Assuming a per voxel probability threshold of $p$=0.001, after 10 000 simulations, a cluster size of 343 re-sampled voxels (i.e., 343mm$^3$) was indicated to correct for multiple comparisons at $p$<0.05. Regional beta-values were extracted and used to perform correlation analyses between BOLD responses and clinical variables (e.g., psychiatric symptoms, IQ and antipsychotic dosage).

*MRI data analyses*

Between-group differences in gray matter (GM) volumes were investigated using voxel-based morphometry (VBM) (Ashburner, 2007; Ashburner & Friston, 2000). We used the *Diffeomorphic Anatomic Registration Through an Exponentiated Lie Algebra* algorithm of the *Statistical Parametric Mapping-12* software (SPM-12; Wellcome Department of Cognitive Neurology), which provides improved registration accuracy compared with conventional VBM (Klein et al., 2009). Analyses were made according to the steps proposed by (Ashburner, 2015). Magnetic resonance images were segmented into GM, white matter and cerebrospinal fluid. GM

population templates were generated from the entire image dataset, and were normalized to the *Montreal Neurological Institute* (MNI) stereotaxic space. Images were modulated to ensure that relative GM volume was preserved following spatial normalization. The voxel sizes for spatially normalized images were $1.5mm^3$. Images were smoothed with an 8mm Gaussian kernel (FWHM). Between-group differences in GM volumes were assessed using independent-samples t-test. VBM data was corrected for participants' total intracranial volume using proportional scaling. The participants' age and IQ were entered as covariates in the model. An initial threshold of $p_{(uncorr.)}<0.001$ was used for the statistical parametric maps of GM between-group comparisons. Based on the inverse of the icbm2tal affine transformation matrix (Laird et al., 2010; Lancaster et al., 2007), fMRI clusters of interests were converted from the Talairach to the MNI (as implemented in SPM) stereotaxic space. These fMRI data-driven ROIs were applied to GM between-group differences using a small volume correction (SVC, as implemented in SPM12) family-wise error (FWE) $p_{(FWE)}<0.05$ corrected threshold. The MATLAB NeuroElf toolbox (http://neuroelf.net) was used for visualization. The open-source image editor GIMP was used to build the figures (http://www.gimp.org).

## Results

### *Clinical Data*

Men with schizophrenia had a lower IQ than healthy men (see Table 1). The two groups did not differ in terms of age, handedness, and ethnicity. There was a non-significant trending effect in the performance on the BART, where schizophrenia patients gained less money than healthy subjects and exploded significantly fewer balloons. Moreover, schizophreniform or

schizoaffective subjects did not differ significantly on these variables from the rest of the SCZ sample.

Table 1. Participant characteristics

| | SCZ (*n*=47) | Healthy (*n*=23) | Significance |
|---|---|---|---|
| Age, mean years (SD) | 34.4 (9.6) | 31.9 (8.2) | *t*=-1.10; *p*=0.28 |
| Handedness, % right | 89.5 | 95.5 | $\chi^2$=1.22; *p*=0.54 |
| Ethnicity, % Caucasian | 80.9 | 87.0 | $\chi^2$=1.54; *p*=0.82 |
| IQ, (SD) | 89.2 (10.8) | 100.7 (15.3) | ***t*=3.00; *p*=0.005** |
| BART Total, $ (SD) | 17.0 (5.2) | 19.3 (5.1) | *t*=1.77, *p*=0.08 |
| Rate of exploded balloon, % (SD) | 23.2 (13.6) | 31.3 (15.9) | ***t*=2.20, *p*=0.03** |
| Diagnoses | 12 SA, 1SZP | - | - |
| Age of onset, mean years (SD) | 22.2 (5.8) | - | - |
| PANSS – 5 factors, (SD) | | | |
| Positive | 9.7 (2.5) | - | - |
| General | 14.6 (4.8) | - | - |
| Disorganized | 7.5 (2.1) | - | - |
| Excited | 7.2 (2.7) | - | - |
| Depressed | 7.9 (2.2) | - | - |
| Clozapine, % | 42.5 | - | - |
| Olanzapine equivalents mg, (SD) | 14.6 (8.7) | - | - |

BART = Balloon Analogue Risk Task; PANSS= Positive And Negative Syndrome Scale; IQ = Intelligence quotient; SA= Schizo-affective disorder; SZP = Schizophreniform; SD = standard deviation. Bold font indicates significant between-group differences.

*fMRI data*

For the decision to Inflate event (main effect), increased activations were observed in the left superior frontal gyrus in schizophrenia patients, relative to healthy subjects (Table 2; Fig. 2). A trending between-group difference was observed in the left superior frontal gyrus for the Inflation event *with parametric modulation* (see Supplementary Material Figure S1). For the Success outcome event (main effect), increased activations were observed in schizophrenia patients, relative to healthy subjects, in the bilateral occipital, left putamen, left precentral and postcentral gyrus (Table 2; Fig. 2). For the Success event *with parametric modulation*, all these regions (including the putamen) were found to be significantly activated across groups (both

schizophrenia patients and healthy subjects), but no between-group differences were observed (see Supplementary Material Figure S2).

For the Win outcome event, increased activations were observed in schizophrenia patients, relative to healthy subjects, in the bilateral putamen, bilateral cingulate gyrus, left middle and superior frontal gyrus, left claustrum, left insula, and the left supramarginal gyrus (Table 2; Fig. 2).

Finally, no associations were found between activations and psychiatric symptoms, olanzapine equivalents, or IQ in schizophrenia. Schizophreniform or schizoaffective subjects did not differ significantly in activations from the rest of the SCZ sample.

Table 2. Differences in activations between schizophrenia patients and controls during reward-related decision-making

| Region | L/R | BA | Talairach | | | T-max | Voxels ($mm^3$) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| Decision to Inflate | | | | | | | |
| [SCZ > Healthy] | | | | | | | |
| Superior frontal gyrus | L | 8 | -12 | 44 | 34 | 4.1 | 654 |
| [Healthy > SCZ] | | | | | | | |
| - | | | | | | | |
| Success | | | | | | | |
| [SCZ > Healthy] | | | | | | | |
| Inferior occipital gyrus | R | 19 | 36 | -76 | -5 | 4.4 | 1517 |
| Middle occipital gyrus | R | 18 | 18 | -88 | 16 | 4.9 | 1980 |
| Putamen | L | - | -24 | 2 | 16 | 4.4 | 1981 |
| Inferior occipital gyrus | L | 18 | -36 | -85 | -2 | 4.1 | 466 |
| Inferior frontal gyrus/ Precentral gyrus | L | 44 | -48 | -1 | 16 | 4.4 | 1384 |
| Postcentral gyrus | L | 40 | -63 | -25 | 19 | 4.3 | 358 |
| [Healthy > SCZ] | | | | | | | |
| - | | | | | | | |
| Win | | | | | | | |
| [SCZ > Healthy] | | | | | | | |
| Putamen | R | - | 24 | 8 | 7 | 4.4 | 894 |
| Cingulate gyrus | R | 32 | 9 | 11 | 34 | 4.3 | 1067 |
| Cingulate gyrus | L | 24 | -9 | 2 | 37 | 4.7 | 1831 |
| Superior frontal gyrus | L | 6 | -9 | -13 | 67 | 4.1 | 439 |
| Putamen/Insula | L | - | -24 | 11 | 13 | 4.3 | 1947 |
| Inferior frontal gyrus | L | 47 | -30 | 8 | -14 | 4.0 | 438 |
| Middle frontal gyrus | L | 9 | -30 | 26 | 34 | 4.6 | 1050 |
| Supramarginal gyrus | L | 40 | -42 | -40 | 31 | 4.5 | 1626 |
| [Healthy > SCZ] | | | | | | | |
| - | | | | | | | |

L/R = left/right hemisphere, BA= Brodmann area; SCZ= schizophrenia

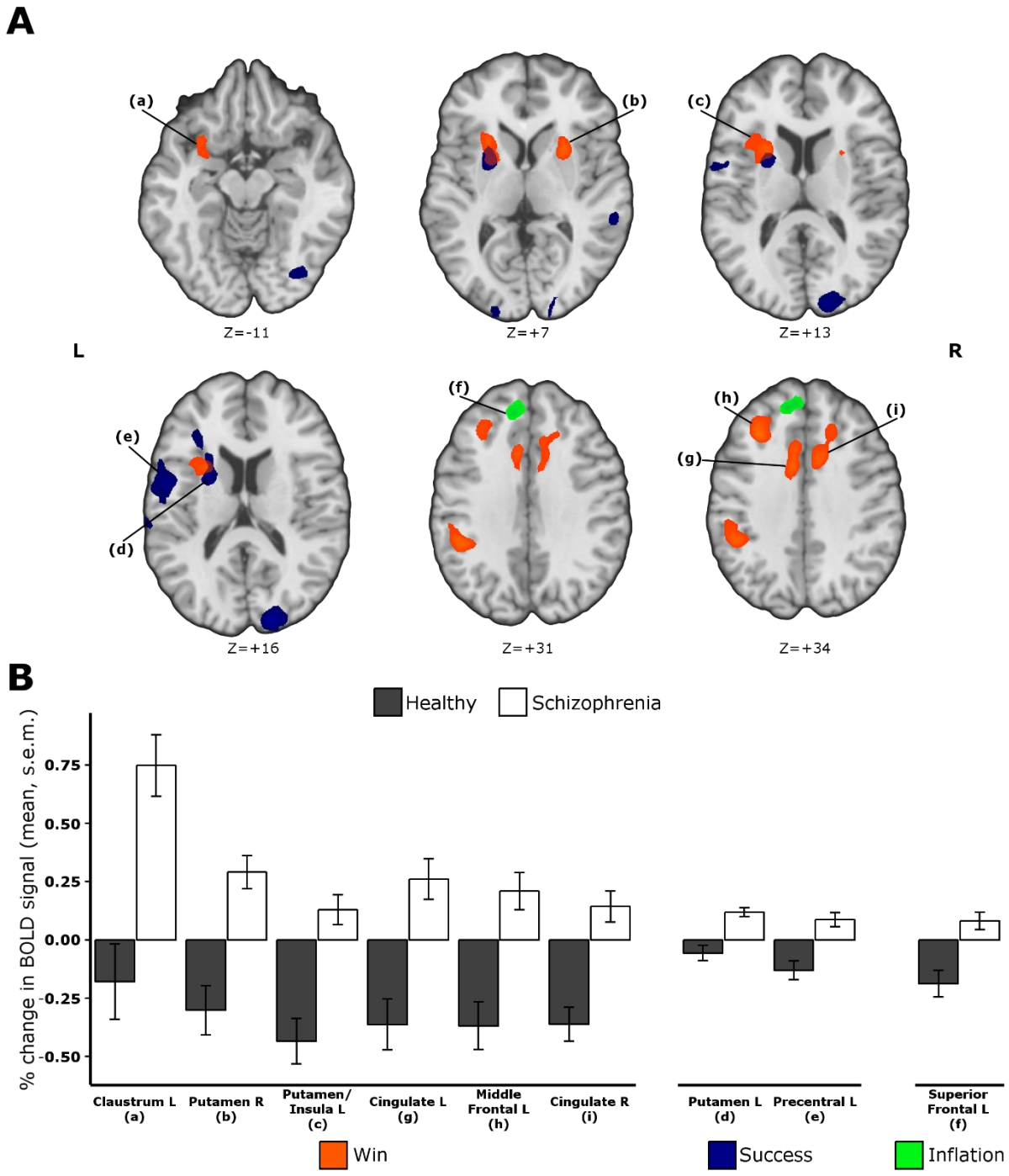


Figure 2. Hyperactivations in schizophrenia patients in comparison to healthy subjects during risky decision-making. A. Between-group differences during the Win event, and B. the associated percent change in BOLD signal by group.
Abbreviations: BOLD, blood oxygen dependent signal; L/R, left/right hemisphere.

*MRI Data*

VBM analyses revealed a widespread decrease in gray matter volume in schizophrenia patients compared to healthy subjects in several bilateral frontal, cingular, insular, and cerebellar regions (see Supplementary Material Table S1). Of the regions significantly impaired in schizophrenia as determined by the functional analyses, we used the putamen, insula, and cingulate gyrus as fMRI data-driven ROIs for subsequent neuroanatomical analyses, given that previous fMRI studies using the BART have shown that these regions are reliably involved in reward-related decision-making (Forster et al., 2016; Galván et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). The ROI analysis of the left putamen/insula [Win event] revealed a significant decrease in insular GM volume in schizophrenia patients compared with healthy subjects (SVC peak $p_{(FWE)}$=0.007, $p_{(uncor.)}$<0.001, $t$=3.98, peak-coordinate (MNI) -35,15,8l; cluster-level $p_{(FWE)}$=0.025) (Figure 3). No between-group differences were observed in other ROIs. Schizophreniform or schizoaffective subjects did not differ significantly in insular volume from the rest of the SCZ sample.

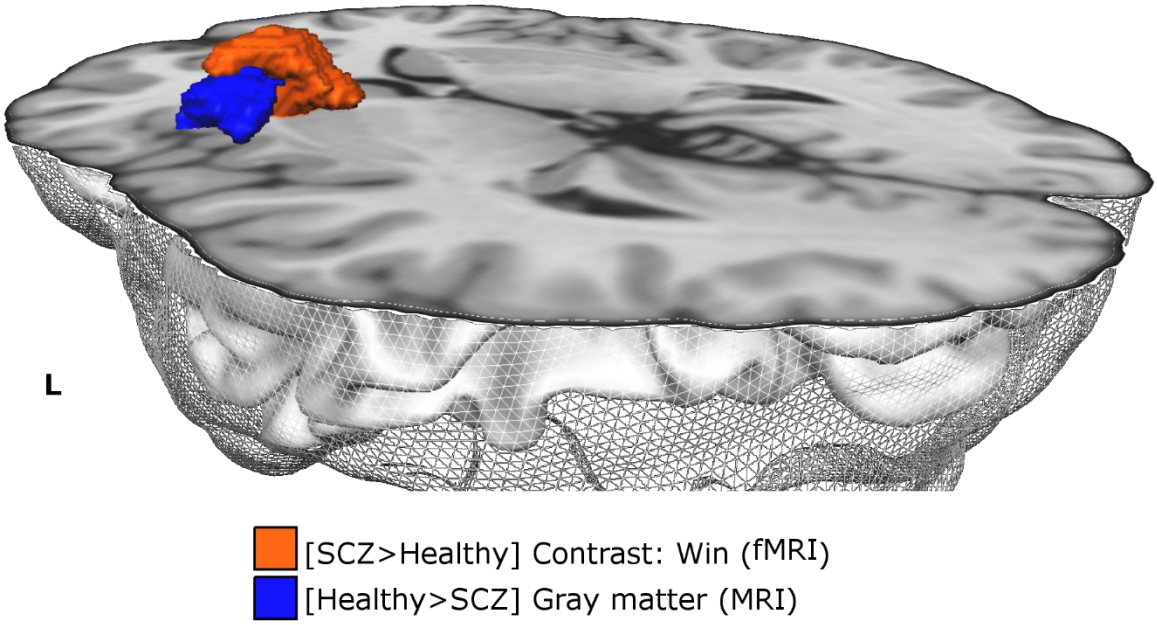


Figure 3. Left anterior insular structural and functional alteration overlap in schizophrenia.
Abbreviations: MRI, magnetic resonance imaging; fMRI, functional MRI; SCZ, schizophrenia, L, left hemisphere.

**Discussion**

To our knowledge, this is the first multimodal neuro-imaging study to employ the BART to investigate both the functional and structural alterations underlying impaired reward-related decision-making in schizophrenia. At the behavioral level, schizophrenia patients displayed risk avoidance, as they made slightly fewer gains and made significantly fewer explosions. Our fMRI analyses revealed functional alterations in schizophrenia patients, notably in the superior frontal gyrus during decision-making, the putamen and precentral gyrus following successful trials, and the bilateral putamen, left insula, bilateral cingulate, superior left claustrum, and middle frontal gyrus when receiving an expected reward [Win event]. We did not observe between-group differences in cerebral activity when assessing Success events modulated by the

probability of explosion. When examining the Success modulated events, we did observe, however, activations across groups in regions such as in the left putamen that are consistent with the results of previous fMRI studies using the BART (Forster et al., 2016; Galván et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). Structural analyses revealed widespread gray matter volume loss in schizophrenia patients when compared to healthy subjects, especially in medial frontal/orbital as well as bilateral cingular and insular regions. We assessed the conjunction between structural and functional alterations, and found a spatial overlap in the left anterior insula specifically, where decreased gray matter volume corresponded with an altered activation in schizophrenia patients during reward processing, when compared to healthy subjects.

Our results show neuro-functional alterations in schizophrenia in brain regions (i.e., putamen, insula, and cingular cortex) that have been consistently found to be involved in reward-related decision-making in several fMRI studies using the BART (Forster et al., 2016; Galván et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). These results are coherent with abundant literature in neuroimaging showing striatal alterations during reward processing in schizophrenia, independently of decision-making processes (Strauss et al., 2014). Interestingly, most of the functional differences were observed during the reward outcome events (Success & Win), and not during the choice/decision periods. Furthermore, the differences in activations were observed in the Success event that was not modulated by the probability of explosion. Increased activations were also observed in sub-cortical regions (e.g., striatum & insula) in schizophrenia during the Win event in the BART, which is a well-predicted outcome having reduced rewarding value, since the participants know they have banked the amount of money that was wagered (Schonberg et al., 2012). Taken together, these observations suggest that between-group differences were mostly driven by an overvaluation of outcome stimuli having

little biological significance that is present from the start (main event), regardless of gain increases. Although the results of the current study might echo the aberrant salience hypothesis of psychosis (Howes & Nour, 2016; Kapur, 2003), it is important to point out that this hypothesis states that psychosis results from the attribution of motivational value to irrelevant stimuli, whereas the current results highlight an over-valuation of stimuli having low motivational value. Regardless of these subtle differences, the current results are novel in that they may explain why schizophrenia patients tend to avoid risk in tasks such as the BART (Cheng et al., 2012; Reddy et al., 2014). That is, reward seeking in these patients may be fulfilled more quickly, even by stimuli with low motivational value. Finally, during the decision to Inflate events, schizophrenia patients displayed increased activations in the medial superior frontal gyrus. Previous fMRI studies have shown that this part of the dorso-medial prefrontal cortex plays a key role in action selection (Rushworth et al., 2004), suggesting that increased neurophysiologic effort is required to make reward-related decisions in schizophrenia.

Another relevant finding of this study is the spatial overlap between structural and functional alterations, as measured by VBM and fMRI respectively, in the left anterior insula in schizophrenia patients. Our results are consistent with recent studies investigating reward-related decision-making in healthy subjects using the BART. Indeed, Helfinstein et al. (2014) have observed that BOLD activity patterns in bilateral anterior insula were reliable predictors of the ability to make safe versus risky choices during the BART. Moreover, Nasiriavanaki et al. (2015) reported a positive correlation between the performance on the BART and gray matter volume specifically in the right anterior insula. These studies suggest that reward-related decision-making, as measured by the BART, is related to both structural and functional features of the anterior insula, which is involved in emotion awareness and has connections with

structures implicated in reward processing such as the anterior cingulate cortex, prefrontal cortex and the limbic system (i.e., amygdala and striatum) (Namkung, Kim & Sawa, 2017). In comparison, the posterior insula has been associated with somatosensory/nociceptive (Segerdahl et al., 2015) and motor information processing (Namkung et al., 2017). The spatial overlap between the functional and structural alterations in this limbic region suggest that anterior insula alterations also pay a key role, along with the striatum, in the impaired ability of schizophrenia patients to make reward-related decisions (Ouzir, 2013). This is an important result given that the spatial overlap is determined within the same pool of participants, especially when a majority of individual neuroimaging studies employing a multimodal approach are unable to establish a spatial correspondence between structure and function in schizophrenia (Isobe et al., 2016). Our main result is coherent with results from Radua et al. (2012) who reported spatially conjoint structural and functional alterations in the anterior insula of first episode psychosis patients in a multimodal neuroimaging meta-analysis of 43 studies (1427 psychosis patients and 1403 healthy subjects).

This study presents certain limitations, as all participants recruited in this study were male. Although this inclusion criterion limits the generalizability of our findings, this choice was based on literature showing sex-differences in decision-making (Reber & Tranel, 2017) and on our objective to reduce sources of heterogeneity. Furthermore, schizophrenia patients were taking antipsychotic medications, which could be a potential confound, as studies have reported that antipsychotic treatment can influence both brain structure (Smieskova et al., 2009) and function (Fusar-Poli et al., 2007). For instance, it has been shown that antipsychotics block dopamine-D2 receptors in the striatum (Kapur et al., 2000). Therefore, some of our results could be explained by the confounding effects of antipsychotics. To account for the potential effect of

antipsychotic medication on our results, olanzapine equivalents were calculated and applied in covariance analyses, and we found that antipsychotics had no influence on our results. In addition, over the quarter of the SCZ sample recruited for this study were schizophreniform or schizoaffective subjects. However, we did not observe significant differences in BART performance and neural activations between these individuals and the rest of the SCZ sample. As for the BART task itself, participants were aware that there were no actual monetary incentives associated with the outcome of the task, although this could have influenced the level to which participants were invested in the task. Unfortunately, no data was gathered on smoking status in the current study. Given that risk-taking is higher in cigarette smokers (Lejuez et al., 2003), the potential confounding effect of smoking status on our result cannot be ruled out. Finally, we could not perform analyses on the explosion events, simply because of their low prevalence. Despite these limits, the results of this study are substantial as they are based on a large sample of schizophrenia patients, using a task that is considered an ecologically valid model to assess reward-related decision-making (Rao et al., 2008), simple to understand, and that allows for the investigation of decision and outcome periods separately (Bogg et al., 2012). Our results are also reinforced by the multimodal coherence of an insular alteration in schizophrenia, which is noteworthy considering the paucity of non-meta-analytic neuroimaging studies that report a spatial overlap between functional and structural dysfunctions in schizophrenia.

To conclude, this is the first multimodal imaging study to investigate reward-related decision-making processing in a large sample of male schizophrenia patients, using the BART. The results indicate increased sub-cortical activations of the striatum and insula during outcome events in schizophrenia patients when compared to healthy subjects, as well as spatially

convergent structural alteration in the left anterior insula. As such, these results may underlie the sub-optimal ability to make reward-related decisions in schizophrenia, which is characterized by risk avoidance. Future studies on risky decision-making in schizophrenia will need to pay attention to uncertainty, since decision-making has been shown to be influenced by uncertainty in healthy populations, and decision-making under uncertainty has been shown to be impaired in schizophrenia (Fujino et al., 2016). Finally, future studies should seek to compare and/or replicate our results in women.

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**Contributors**

AT wrote the manuscript, did the brain imaging analysis; AD was involved in study design, patient recruitment and assessment, as well as provided critical comments about the manuscript. OLipp was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; ES was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; PL was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; ML was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; OLungu was involved in brain imaging analysis and provided critical comments about the manuscript; SP was involved in study design, brain imaging analyses, writing the manuscript, as well as provided critical comments about the manuscript.

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## Conflict of Interest

AD and SP are holders of grants from Otsuka Pharmaceuticals and HLS Therapeutics unrelated to the current study. AT, OLipp, ES, PL, ML, OLungu reported no biomedical financial interests or potential conflicts of interest.

## Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.03.007.

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**Supplementary Material**

Table S1. Differences in gray matter between schizophrenia patients and healthy subjects

| Region | L/R | BA | MNI | | | T-max* | Voxels ($mm^3$) |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| [ Healthy > SCZ] | | | | | | | |
| Medial orbitofrontal gyrus/ Medial superior frontal gyrus/ Anterior cingulate gyrus | L/R | 11/25 | 5 | 41 | -14 | 6.15 | 10486 |
| Postcentral gyrus/ Precentral gyrus/ Supramarginal gyrus | L | 6 | -57 | 0 | 41 | 5.04 | 5964 |
| Insula/ Inferior frontal gyrus | L | 47/13 | -42 | 21 | -8 | 5.01 | 3470 |
| Cerebellum | R | - | 39 | -59 | -45 | 4.96 | 5235 |
| Inferior orbitofrontal gyrus/ Insula | R | 47/13 | 41 | 23 | -20 | 4.78 | 1954 |
| Inferior frontal gyrus/ Middle frontal gyrus | L | 46/9 | -51 | 30 | 24 | 4.68 | 2788 |
| Cerebellum | L | - | -29 | -75 | -39 | 4.31 | 4914 |
| Middle frontal gyrus | R | 46 | 51 | 36 | 29 | 4.24 | 1866 |
| Calcarine sulcus/ Lingual gyrus | L | 18 | -2 | -89 | -17 | 3.94 | 2089 |
| Cerebellum | L/R | - | -2 | -54 | -60 | 3.82 | 1397 |
| [ SCZ > Healthy] | | | | | | | |
| - | | | | | | | |

L/R = left/right hemisphere, BA= Brodmann area; SCZ= schizophrenia; MNI = Montreal Neurological Institute

* voxel-wise $p<0.001$ uncorrected, cluster threshold = 400 voxels (1.5 $mm^3$).

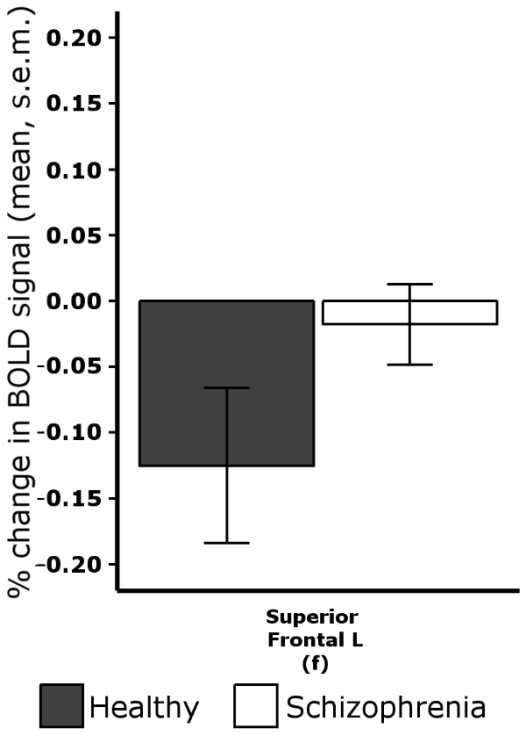


Figure S1. Percent change in BOLD signal by group during the Inflation event modulated by the probability of explosion.
Abbreviations: BOLD, blood oxygen dependent signal; L, left hemisphere.

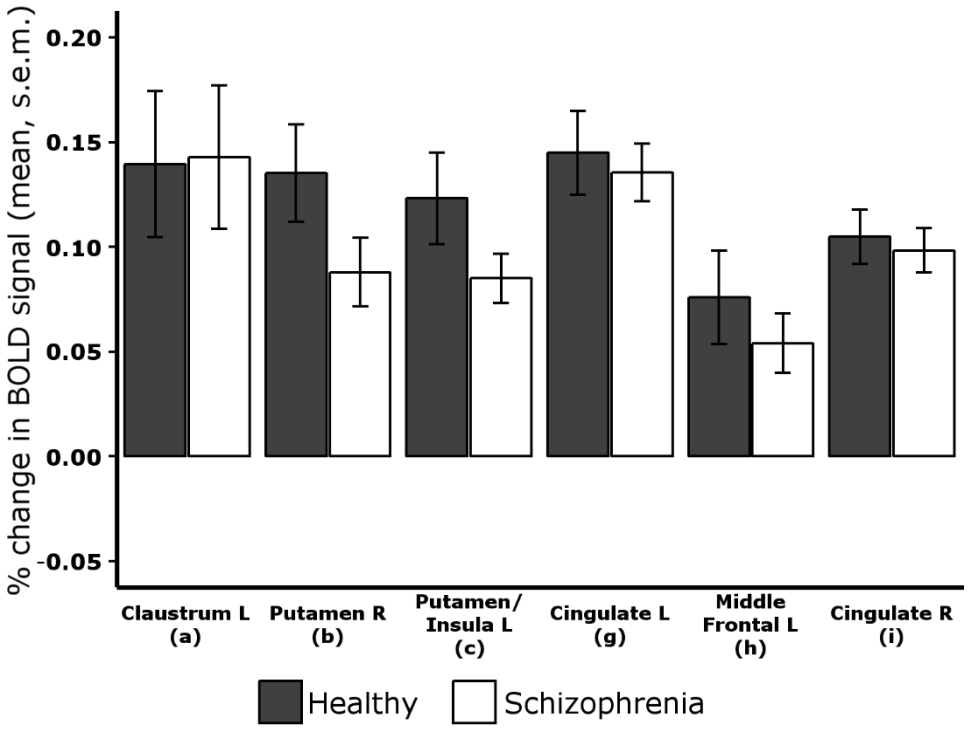


Figure S2. Percent change in BOLD signal by group during the Success event modulated by the probability of explosion.
Abbreviations: BOLD, blood oxygen dependent signal; L/R, left/right hemisphere.

# 6 Discussion

The aim of this thesis was to investigate the neurocognitive basis of aggressive behaviors in schizophrenia using task-based functional magnetic resonance imaging. We hypothesized deficits in neural systems underlying cognitive control, emotion processing, and reward processing specific to individuals with schizophrenia and a history of aggressive behaviors as compared to non-violent individuals with schizophrenia and healthy subjects (Fanning et al., 2017; Leclerc et al., 2018; Stahl, 2014). We observed disrupted anterior cingular functional activity (i.e., hyperactivity; Tikasz et al. (2016)) and connectivity patterns (i.e., increased connectivity with frontal regions and decreased with subcortical regions; Tikàsz et al. (2020)) during negative emotion processing in aggressive men with schizophrenia. Additionally, men with schizophrenia and a history of violence failed to recruit a core region of the cognitive control network when inhibiting motor responses while presented with anger stimuli as evidenced by a reduced activation of the DLPFC (Tikasz et al., 2017). We did not find significant neural activity alterations during positive stimuli (Tikasz et al., 2016) and reward processing (Tikàsz et al., 2019) differentiating aggressive and non-aggressive individuals with schizophrenia. The strengths of our studies include targeted functional investigations of cognitive and emotional states relevant to the emergence of aggressive behaviors using relatively large samples, appropriate control groups, uniform criteria for aggression, and whole brain analyses.

## 6.1 Emotion processing

One of our principal observations is the ventral ACC hyperactivation elicited by negative pictures in men with schizophrenia and a history of violence relative to non-aggressive psychotic

and non-psychotic men (Tikasz et al., 2016). We further found dorsal ACC connectivity patterns specific to SCZ+V during the same experimental condition (Tikàsz et al., 2020). These results suggest anterior cingular deficits concordant with neurobiological mechanisms associated with impulsive violence in non-psychotic (Coccaro et al., 2011) and psychotic individuals (Leclerc et al., 2018). The ACC is involved in social processes (Green et al., 2015), response inhibition (Puiu et al., 2020), and is essential to neural circuits underlying socioemotional information integration and emotion regulation in aggressive behaviors (Coccaro et al., 2011). ACC thinning was recently associated with hostility and poor impulse control in schizophrenia (Wong et al., 2020). An underactive ACC was reported during motivationally and emotionally significant tasks in CD (Alegria, Radua & Rubia, 2016) and negative stimuli perception in individuals presenting antisocial behaviors as well (Dugré et al., 2020). Whether ACC hyperactivity observed in our analysis as opposed to hypoactivation reported in the literature is the consequence of the population investigated or due to task heterogeneity relative to other studies remains to be determined. Nevertheless, ACC involvement signifies a broader emotion processing and regulation deficit among aggressive individuals. The ACC is a neural relay structure where affective (rACC) and cognitive (dACC) influences are integrated to impact response behavior (Gasquoine, 2013; Rosell & Siever, 2015). The dACC is furthermore a core node of the salience network (Uddin, 2016). A functional dysregulation may contribute to a difficulty in combining these aspects of negative emotion processing and lead to aggression.

We did not observe significant amygdalar differences in functional activity (Tikasz et al., 2016) or connectivity (Tikàsz et al., 2020) during emotion perception in patients with a history of violence. The amygdala is thought to be implicated in the abnormal negative emotional stimuli processing (Davidson et al., 2000) central to prevailing models of antisocial

behaviors (Raine, 2018) and also reported in schizophrenia (Dong, Wang, Jia, et al., 2018). Viewing negative pictures elicited an expected amygdalar response in SCZ+V and healthy controls in our studies, which did not differ between the 3 groups (Tikasz et al., 2016). Notably, Dugré et al. (2020) also observed a lack of significant amygdalar differences in CD/ASPD in a recent meta-analysis. A range of negative stimuli have been previously examined in aggression and anger specifically was reported to be a strong emotional predictor of violence in offenders (Chereji et al., 2012) and in schizophrenia spectrum disorders (Reagu et al., 2013). Presenting a narrower range of anger stimuli might have potentially exacerbated diverging amygdalar reactivity between the groups investigated in our study. These results could indicate a maladaptive regulation in aggressive individuals (Roberton et al., 2012, 2014). In fact, structural brain imaging in aggressive individuals with schizophrenia show corresponding impairments, such as reduced cortical matter, in regions involved in emotional evaluation and control rather than generation of aggressive impulses such as the amygdala (Leclerc et al., 2018). Therefore, differences between violent and non-violent individuals might be in their capacity to modulate perceived emotions, as suggested by our results.

Together with significant differences in between-groups neural activity, we reported a lack of group differences in the subjective experience of emotions (Tikasz et al., 2016). Explicit emotional experience has not been found to be affected in schizophrenia (Green et al., 2015; Llerena, Strauss & Cohen, 2012) despite clinical observations highlighting impaired emotional expression (i.e., affect flattening) in this patient population (Potvin, Tikàsz & Mendrek, 2016). Furthermore, individuals with schizophrenia with or without a history of violence conveyed experiencing a marginally increased emotional reaction to the neutral images than healthy subjects in our study (Tikasz et al., 2016). This is consistent with meta-analytic findings of

increased self-reported arousal to neutral stimuli in individuals with schizophrenia (Llerena et al., 2012), as non-threatening cues are posited to be assigned aberrant salience (Dugré et al., 2019; Potvin et al., 2016). Meta-analysis of neuroimaging data in individuals with schizophrenia have shown significant differences in studies employing emotional (e.g., reduced ACC activity; Taylor et al. (2012)) and neutral (e.g., increased amygdala activity; Dugré et al. (2019)) stimuli. Therefore, the preserved explicit subjective emotional experience, increased self-reported arousal to neutral stimuli, and altered neural processing of emotions observed (Tikasz et al., 2016) are in-line with the literature and highlight the importance of distinguishing the specific components of emotionality that are impacted in this psychopathology (Kring & Moran, 2008). This pattern was suggested to indicate impaired reflective and preserved reflexive social cognitive processes in schizophrenia, the former including emotional perception/processing/ regulation and the latter emotion experience (Green et al., 2015). The reason for this could be the increased mental effort associated with reflective as opposed to reflexive processes, although this remains poorly understood and requires further investigations (Green et al., 2015; Llerena et al., 2012).

## 6.2 Cognitive control

In addition to group-specific ACC results during negative emotion processing (Tikàsz et al., 2020; Tikasz et al., 2016) we found DLPFC under-recruitment associated with response inhibition in the context of viewing faces displaying anger in men with schizophrenia and a history of aggressive behaviors (Tikasz et al., 2017). Consistent with these results, we also found aberrant connectivity patterns in this region during negative image processing in a separate sample of aggressive men with schizophrenia (Tikàsz et al., 2020). Go-NoGo elicited functional neural activity was observed in non-psychotic offenders to improve violence and recidivism

prediction (Aharoni et al., 2013; Kiehl et al., 2018). These paradigms were also utilized to investigate neural correlates of aggression in schizophrenia, though yielding limited results (Barkataki et al., 2008; Joyal et al., 2007). This is the first fMRI study in this patient population to operationalize a context favorable for the emergence of violent behaviors by combining impulse inhibition and anger processing in an affective Go-NoGo task (Bertsch et al., 2020; Coccaro et al., 2011; Robinson et al., 2019; Stahl, 2014).

The DLPFC is a core region of the cognitive control network associated with attentional flexibility and inhibition (Niendam et al., 2012). It was consistently shown to be underactivated in individuals presenting antisocial behaviors (Alegria et al., 2016) and to be similarly dysregulated in schizophrenia (Crossley et al., 2016; Minzenberg et al., 2009). Our results are in-line with these findings and provide a plausible neurocognitive mechanism for the significant association between angry affect and violence in schizophrenia spectrum disorders (Reagu et al., 2013). A deficit in neural activity associated with anger processing is especially relevant given the impaired emotion processing and regulation in individuals with antisocial behaviors (Hodgins et al., 2013; Raine, 2019), schizophrenia (Green et al., 2015), and aggressive individuals with schizophrenia (Bulgari et al., 2020; Sedgwick et al., 2017).

Response time was not evaluated in this or the other studies in the present thesis. Nevertheless, the relation between response time and the significantly higher self-reported impulsivity we observed in both violent and non-violent individuals with schizophrenia may have been of interest. A meta-analysis of inhibitory cognitive tasks, including Go-NoGo, found significantly slowed response time and marginally more commission and omission errors in individuals with schizophrenia when compared to healthy subjects (Wright et al., 2014), the latter error results being consistent with our observations (Tikasz et al., 2017). A slowed reaction

time during response inhibition was further associated with aggressive behaviors in a large cohort of non-psychiatric violent offenders, which is suggestive of an executive function deficit in inhibiting aggressive behaviors (Wallinius et al., 2019). A slower response time during inhibitory cognitive tasks was likewise observed in a small sample of violent offenders (Enticott, Ogloff, Bradshaw, et al., 2008) and non-violent individuals (Enticott, Ogloff & Bradshaw, 2008) with schizophrenia. However, cognitive inhibitory impairments, as measured by response time, were not associated with self-reported impulsivity in schizophrenia (Enticott, Ogloff & Bradshaw, 2008; Enticott, Ogloff, Bradshaw, et al., 2008). Consequently, cognitive inhibition deficits in this patient population may be unrelated to the self-reported impulsivity and impulsive behaviors often associated with violence (Enticott, Ogloff, Bradshaw, et al., 2008). Based on these results, slower reaction times could have been expected in individuals with schizophrenia and a history of aggressive behaviors in our study, which would have provided a complementary measure of inhibitor deficit rather than impulsivity.

Taken together, our results highlight the interaction between emotional processing and cognitive control to be fundamental for understanding the neurobiology of aggression and violence in schizophrenia as well as contribute to the current state of knowledge by providing neurofunctional bases associated with these processes (Tikàsz et al., 2020; Tikasz et al., 2016; Tikasz et al., 2017). Our investigations join others in support of psychotherapeutic interventions targeting emotion regulation in interpersonal situations for individuals with schizophrenia displaying violent/aggressive behaviors (Adams & Yanos, 2020). This includes cognitive remediation therapy given the positive effect of skills training in moderating social cognitive deficits in aggressive individuals with schizophrenia (Darmedru et al., 2017). A reduction in aggression was reported in patients with schizophrenia following facial affect

recognition training (Byrne et al., 2015), further highlighting the clinical implications of our results.

## 6.3 Reward processing

Individuals with schizophrenia were previously found to have suboptimal reward processing (Brown et al., 2015) which was suggested to be mediated by blunted striatal activity (Radua et al., 2015). Impaired decision-making and reward processing were also proposed to be mechanisms for aggression (Bertsch et al., 2020; Fanning et al., 2017). In the last study, we investigated reward-related decision-making in schizophrenia using multimodal neuroimaging (Tikàsz et al., 2019). The same sample of men with schizophrenia with and without history of violence was utilized for this purpose (Tikàsz et al., 2019) as in the third study (Tikasz et al., 2017). The Balloon Analogue Risk Task was employed as it allowed for the separate analysis of reward related decisions and outcomes (Bogg et al., 2012).

We did not find differences in neural activations between violent and non-violent patients with schizophrenia during the BART (unpublished). Characteristics of violent and non-violent participants with schizophrenia in Tikàsz et al. (2019) can be found in Tikasz et al. (2017). Individuals with schizophrenia adopted a conservative rather than impulsive approach regardless of history of aggressive behaviors. We further observed increased striatal and insular activity in individuals with schizophrenia during rewarding outcomes (Tikàsz et al., 2019). The hyperactivations were independent of risk and were associated with events of low motivational value and known outcome, features indicative of reward overvaluation during decision-making. Our results are comparable to others reporting suboptimal decision-making in schizophrenia using this paradigm (Boka et al., 2020; Cheng et al., 2012; Luk et al., 2019; Purcell et al., 2021). Purcell et al. (2021) suggested the performance of individuals with schizophrenia on the BART

to be reflective of an inability to discern risk or risk aversion. These results contrast with the increased frequency of gambling and substance use disorders reported in schizophrenia (Fortgang, Hoff & Potenza, 2018) suggestive of a propensity for pathological impulsivity (Reddy et al., 2014). Impulsive reactions were also proposed to be integral to aggression in schizophrenia as shown by the tendency to resort to sharp objects such as knives in extreme cases of violence (Minero, Barker & Bedford, 2017). Overall, our results evidence altered risk decision-making but do not capture the clinically observed impulsivity and relation to aggression in this psychopathology (Hoptman, 2015).

Models of aggression have stipulated a striatal mediated heightened sensitivity to rewarding stimuli in aggressive individuals (Raine, 2018). However, a transdiagnostic meta-analysis of reward processing fMRI tasks showed no significant associations with antisocial traits (Dugré et al., 2020). Clear reward processing impairments were likewise not demonstrated in antisocial youth in behavioral studies using the BART and similar tasks (Byrd, Loeber & Pardini, 2014). Dysregulated striatal activity in schizophrenia could also represent a deficit in reinforcement learning rather than a blunted response to reward (Chase et al., 2018; Radua et al., 2015). Recent behavioral studies reported concordant results of ineffective risk-reward learning across trials of the BART in individuals with schizophrenia (Boka et al., 2020) which could explain poor decision-making (Heerey, Bell-Warren & Gold, 2008). Therefore, impulsivity related impairments in aggression and schizophrenia might not be directly associated with reward-processing. Alternatively, the association between reward processing and violence might not have been captured in this study as the relationship could be more robust with instrumental violence (Blair, 2016). We did not measure whether the participants recruited in our sample were more prone to reactive or predatory violence.

Punishment (e.g., monetary-loss) and reward are reinforcement learning processes served by comparable neural circuits including the striatum, insula, and ACC (Dugré et al., 2018). Preserved punishment sensitivity in schizophrenia (Cheng et al., 2012) and punishment insensitivity in antisocial individuals (Byrd et al., 2014) were reported in behavioral studies. This implies a possible negative reinforcement related distinction between aggressive and non-aggressive individuals with schizophrenia. Unfortunately, the BART is reward focused (Byrd et al., 2014) with few loss events which did not allow for their analysis in our study (Tikàsz et al., 2019). A systematic review of decision-making paradigms suggested an inability to anticipate punishment in mentally ill violent offenders (Jones et al., 2019). However, performance on the popular risk-taking Iowa Gambling Task did not significantly differentiate offenders with mental illnesses from healthy subjects in a meta-analysis (Jones et al., 2019) or predict impulsive aggressive behaviors leading to seclusion in a forensic inpatient setting (Bass & Nussbaum, 2010).

Impulsivity is a multifaceted concept with some factors perhaps better suited for assessing aggression in schizophrenia (Hoptman, 2015). Negative urgency represents the tendency for rash behaviors as a consequence of intense negative affect (Whiteside & Lynam, 2001) and was significantly associated with aggression in a transdiagnostic meta-analysis (Bresin, 2019). Results from our group (Tikàsz et al., 2020; Tikasz et al., 2016; Tikasz et al., 2017) and others (Reagu et al., 2013) further support negative affect processing as an important component of aggression in schizophrenia. Hoptman et al. (2014) found a significant relation between aggression and negative urgency in individuals with schizophrenia, with both altered prefrontal structural and resting-state functional neuroimaging associated with high urgency. Therefore, emotion-based impulsivity seems relevant to the emergence of aggressive behaviors

in this patient population (Adams & Yanos, 2020). Future investigations of aggression mechanisms could also expand on concepts contextualizing reinforcement learning and impulsivity in negative emotionality, such as provocation (Krämer et al., 2007) and frustration (Bertsch et al., 2020).

## 6.4 Limitations

### 6.4.1 Medication

Our studies present with certain limitations. Participants with schizophrenia were medicated with antipsychotic drugs across the 2 samples recruited. Neuroleptics were reported to have an effect on prefrontal and striatal functional brain activity and gray matter volume in individuals with schizophrenia (Haijma et al., 2012; Vita et al., 2019), potentially confounding the outcomes observed. Chlorpromazine and olanzapine equivalencies employed in our analyses were shown to be inconsistent across drugs (Patel et al., 2013) rendering dosage interpretations problematic (Potvin & Tikàsz, 2015). We were unable to substitute for $D_2$ receptor occupancies as dose-response curves have not been calculated for all antipsychotics taken by the participants (Davis & Chen, 2004). Nevertheless, the dosages were not found to covary or correlate with functional and structural results reported in our studies. The number of subjects receiving clozapine was also not different between violent and non-violent groups of participants with schizophrenia.

### 6.4.2 Violence definition

Participants in our violent groups reported a history of armed aggression resulting in injuries or death (Tikasz et al., 2016), as well as punching, stabbing, shooting, and homicide (Tikasz et al., 2017). Neuroimaging studies in schizophrenia have also employed other operationalizations of violence including particular behaviors, conviction, and comorbid disorders (Widmayer,

Borgwardt, et al., 2018; Widmayer, Sowislo, et al., 2018). The interchangeable use of these non-mutually exclusive heterogenous definitions in the literature (Hodgins et al., 2013) contributes to the between-study inconsistency of neuroimaging results (Fjellvang et al., 2018; Lamsma et al., 2017) and poor treatment response of aggression in schizophrenia (Volavka & Citrome, 2008; Volavka & Citrome, 2011).

Motivation based categories of aggression, specifically the reactive/impulsive form, are the primary focus of transdiagnostic neurobiological research (Coccaro et al., 2011). The emphasis on impulsive over proactive/instrumental violence is justified by the higher incidence in forensic settings (Stahl, 2014). Aggression is assumed to be impulsive in the present thesis and studies alike (Leclerc et al., 2018), even though the most common type of behavior has not been established in schizophrenia (Hodgins et al., 2013). A single neuroimaging study observed lower cortical gray matter volumes spreading beyond the temporal lobe in premeditated than impulsive forensic patients with schizophrenia when compared to non-violent patients (Kuroki et al., 2017). As neural correlates are likely to be different (Rosell & Siever, 2015), it is pertinent to characterize the aggression type in participants with schizophrenia (Fjellvang et al., 2018).

The prominent model of violence in schizophrenia distinguishes individuals with and without trait aggression based on a substantial minority of patients reporting conduct disorder during childhood (Hodgins, 2008; Kim-Cohen et al., 2003). Violent behaviors were observed twice as frequently in this group than in patients without a history of CD (Swanson et al., 2008). Most neuroimaging studies, including ours, have not reported state/trait measures of violence or recruited a group of non-psychotic violent/CD individuals (Fjellvang et al., 2018). Comorbid CD/ASPD in schizophrenia are proposed to represent a unique subgroup given the lack of difference in positive psychotic symptomatology when compared to individuals with

schizophrenia without a history of violence (Bo et al., 2011) or CD (Hodgins et al., 2013; Schiffer et al., 2013), and shared neurocognitive profile with non-psychotic violent/CD individuals (Hodgins, 2017; Hodgins et al., 2013). IQ, memory, executive function, and facial affect recognition deficits (Sedgwick et al., 2017) as well as most brain alterations (Leclerc et al., 2018; Yang & Raine, 2009) are comparable in violent psychotic and non-psychotic individuals. In fact, individuals with schizophrenia and history of CD resemble individuals with ASPD in gray matter volumes (Schiffer et al., 2013) and neural activation during emotional/mental state attribution (Schiffer et al., 2017). Nevertheless, investigations of this subgroup remain scarce (Sedgwick et al., 2017), use small samples (Barkataki et al., 2005; Silver et al., 2005), and are inconsistent between-studies (Naudts & Hodgins, 2006; Soyka, 2011). Relying on this classification could also produce contradictory results (Fanti, 2018) due to the variety of aggressive and non-aggressive behaviors falling under CD and ASPD (American Psychiatric Association, 2013b). For instance, emotional dysregulation and low verbal abilities were associated with physical aggression as opposed to lower inductive reasoning and higher verbal abilities being associated with theft in adolescents (Barker et al., 2011). More narrowed categorization considering behavioral specificities might be needed to account for these differences (Séguin, Pinsonneault & Parent, 2015). The absence of a non-mentally ill violent/CD group can render the independent contribution of aggressivity and schizophrenia difficult to elucidate in the studies presented in the context of this thesis and the associated literature. However, based on available evidence suggesting similar neurocognitive characteristics between psychotic and non-psychotic violent individuals, the benefits of such a group appear limited. Nevertheless, the presence and severity of persistent patterns of antisocial behavior in participants should be clarified in future studies (Dugré et al., 2020; Fjellvang et al., 2018).

Controlling for psychopathic traits was proposed to help differentiate the effect of psychosis amongst aggressive individuals (Kolla et al., 2021). ASPD and psychopathy were suggested to denote the presence of criminality/aggression and the personality traits at risk of such behaviors respectively (Bo et al., 2011). A multivariate analysis showed patterns of gray matter volume to differ among psychotic and non-psychotic offenders matched for psychopathy (Kolla et al., 2021). However, the majority of neuroimaging investigations have not evaluated patients for these traits (Widmayer, Borgwardt, et al., 2018; Widmayer, Sowislo, et al., 2018; Yang & Raine, 2009). The relationship between psychopathy and violence is also inconsistent (Coid, Ullrich & Kallis, 2013) despite associations with violence in psychotic (Rund, 2018) and non-psychotic populations (Bergstrøm & Farrington, 2021). Moreover, two major risk assessment instruments have reduced their reliance on (VRAG, Harris et al. (2015)), or abstained from (HCR-20, Douglas et al. (2013)), the Psychopathy Checklist for evaluating violence and reoffending. Therefore, the advantage of assessing psychopathic traits in aggressive individuals with schizophrenia is uncertain.

Overall, our definition of violence and omission of violent non-mentally ill group are consistent with available neuroimaging studies in schizophrenia (Widmayer, Borgwardt, et al., 2018; Widmayer, Sowislo, et al., 2018). Future investigations would benefit from a finer parsing of aggressive behaviors with discrete typologies and corresponding neurocognitive profiles. Standardization in terms of specifying behavior type/motivation and measuring state/trait violence would allow for better comparison across studies (Fjellvang et al., 2018).

### 6.4.3 Gender

All participants recruited in the context of this thesis were male. The contribution of female gender both as a biological and psychosocial factor has been understudied in the development

of aggressive behaviors in schizophrenia, mirroring the bias in the violence literature (Hodgins et al., 2013; Wang et al., 2017). Reporting in the United States show over 90% of homicides to be perpetrated by men (Fox & Fridel, 2017). Given that women are less likely than men to adopt serious violent or aggressive behaviors, there is less urgency to investigate gender-specific violence (Robbins, Monahan & Silver, 2003). This might carry greater consequences in schizophrenia as a meta-analysis reported a 19.9 times higher risk for violence in women with psychosis compared to without after controlling for potential confounding variables (Fazel et al., 2009). The prevalence of CD in childhood was also estimated to be 15 times higher among women with schizophrenia as compared to non-psychiatric populations (Hodgins, 2017). Furthermore, positive psychotic symptoms were suggested to have a larger effect in increasing the likelihood for assault (Krakowski & Czobor, 2004) and violence was more often directed towards family members in women than in men (Hachtel, Nixon, et al., 2018; Robbins et al., 2003). Therefore, gender as a factor in violence is not benign and indicates an increased potential for violence with differential patterns of factors leading to specific types of behaviors in women with schizophrenia (Hodgins et al., 2013). To date, a small minority of neuroimaging studies investigating aggressive behaviors in schizophrenia have included female participants and none have analyzed gender related effects (Leclerc et al., 2018; Widmayer, Borgwardt, et al., 2018; Widmayer, Sowislo, et al., 2018). In line with the need for more refined typologies, the mechanisms underlying gender differences should be investigated to allow for a better understanding of key aspects that are involved in the emergence of aggression in schizophrenia.

## 6.5 Future directions

Risk assessment establishing potential for aggressive behaviors in individuals with psychiatric disorders remains a public health concern given the significant portion of violence and crime

associated with severe mental illness (Arseneault et al., 2000; Fazel & Grann, 2006). This is particularly critical for individuals with schizophrenia spectrum disorders as they constitute over half of the forensic psychiatric population (Jansman-Hart et al., 2011) and are at substantially elevated risk for violence (Brennan et al., 2000; Whiting et al., 2021). Prior to the MacArthur Violence Risk Assessment Study (Monahan et al., 2001), risk stratification was primarily founded on unaided clinical evaluation which were estimated to yield an inaccurate judgement in up to 2 out of 3 cases (Monahan, Brodsky & Shan, 1981). Contemporary assessment methods now include over 200 actuarial and structured clinical instruments (Falzer, 2013; Singh, Desmarais, et al., 2014) with marginally improved predictive validity (Douglas et al., 2017). There still is a high probability for imprecise classification with 2 to 4 patients needing to be detained or committed to prevent a single re-occurrence of violent behavior (Fazel et al., 2012; Jeandarme et al., 2017; van Heesch et al., 2016). General actuarial and structured clinical tools were found to have similar discriminatory capabilities (Fazel et al., 2012; Yang, Wong & Coid, 2010) in various populations (Glover et al., 2017; Jaber & Mahmoud, 2015) and be least suited for evaluating high risk of recidivism (Ryan et al., 2010; Singh, Fazel, et al., 2014). In fact, lower accuracy of both actuarial (VRAG, Grann, Belfrage and Tengström (2000); Tengström (2001)) and structured clinical instruments (HCR-20, Ivgi et al. (2015); Michel et al. (2013)) was observed in samples constituted exclusively of individuals with schizophrenia. Poor performance causing stigmatization of mis-evaluated/sentenced individuals (Douglas et al., 2017; Large et al., 2011) and lack of strong supporting evidence in schizophrenia (Singh, Serper, et al., 2011) have led to the utility of risk assessment tools to be reconsidered in this patient population.

Existing instruments were found to function better for screening-out low-risk individuals than prognosticating (Fazel et al., 2012) and to have higher predictive validity when designed for a specific population (Singh, Grann & Fazel, 2011). An improved accuracy and excellent negative predictivity were reported in instruments such as the Oxford Mental Illness and Violence tool which was developed expressly for evaluating individuals with schizophrenia (Fazel et al., 2017). Despite accounting for their limitations, risk assessment instruments have reached a ceiling with regards to their predictive power (Coid et al., 2011). Complementary factors such as biomarkers for violence were suggested to likely improve risk evaluation (Poldrack et al., 2017; Sedgwick et al., 2016). These novel markers should be examined as to whether they provide an incremental predictive accuracy over traditionally established factors identified in the literature including substance use, and history of criminal/aggressive behaviors (Witt et al., 2015). Notably, only 1 of 10 structured instruments assessing aggression in schizophrenia screens for a neurobiological marker (i.e., history of head injury; Singh, Serper, et al. (2011)).

Even with an increase in accuracy, the inclusion of biomarkers in risk assessment would not necessarily yield meaningful predictions (Aharoni et al., 2014). One of the principal caveats of currently employed structured instruments is the extension of group derived estimates to single subject prediction for inferring the reoccurrence a discrete event (Douglas et al., 2013; Faigman, Monahan & Slobogin, 2014). Estimates with wide confidence intervals at the group level translate to larger error margins at the patient level that may not be interpretable (Hart, Michie & Cooke, 2007). Employing statistical methods that are better adapted for individualized prediction was proposed to in part solve the issue (Singh, Fazel, et al., 2014). The appeal for

machine learning algorithms allowing to tailor health care to individual patients has grown for this reason (Beam & Kohane, 2018).

A recent multivariate prediction model of 1-year remission and recovery in first episode psychosis based on sociodemographic and clinical variables achieved comparable accuracy as tools commonly used in other medical fields (Leighton et al., 2019). Single subject prediction using structural or functional MRI data showed a mean accuracy >80% for correctly distinguishing individuals with schizophrenia from healthy subjects in a comprehensive review (Arbabshirani et al., 2017), evoking the possibility for brain-based multivariate characterization of mental illness (Rashid & Calhoun, 2020). Although encouraging, there is no conclusive evidence for the benefit of machine learning algorithms such as classification trees, random forests, artificial neural networks, and support vector machines over traditional logistic regression in medical prediction (Christodoulou et al., 2019). Multivariate statistics may also be less accepted in clinical applications due to their decreased interpretability (Whiting & Fazel, 2020) stemming from the loss of direct relationship between the variables evaluated and outcome (Spivak & Shepherd, 2020). Such algorithms do not necessarily provide for a mechanistic understanding which also limits the possibilities for developing risk-management interventions (Tortora et al., 2020). Furthermore, small sample sizes and low number of sites/sources can negatively impact classifier performance (Arbabshirani et al., 2017) and result in overfitting (Bzdok & Meyer-Lindenberg, 2018). Nevertheless, the combination of statistical approaches adapted for individualized prediction with neural biomarkers are thought to be at the foundation of personalized psychiatry (Passos, Mwangi & Kapczinski, 2019) and could be valuable in forensic psychiatry (Tortora et al., 2020).

Classification algorithms relying on socio-clinical variables were found to predict violence (Wang et al., 2020) and recidivism (Kirchebner, Günther & Lau, 2020) in forensic patients with schizophrenia spectrum disorders with equal or increased accuracy to other risk assessment instruments. Genetic, neural, hormonal, metabolic, and physiological dysregulations were candidate markers previously studied in offenders, some with positive preliminary results (Glenn & Raine, 2014). Neuroimaging in aggression or offending prediction was evaluated in few samples only (Tortora et al., 2020). Aharoni et al. (2013) found the reduced functional activity of the ACC during failed response inhibition (i.e., commission error) in a Go-NoGo task to approximately double the likelihood of rearrest within 4 years of release. The neurofunctional marker provided an incremental utility above age and psychopathic personality traits in a sample of 96 non-psychiatric male offenders (Aharoni et al., 2014). In a subsample ($n$ = 45) of these participants, combining error positivity measured by event-related potentials acquired during a separate Go-NoGo session with ACC hemodynamics showed multimodal neuroimaging to further increase predictive accuracy of rearrest (Steele et al., 2015). In a large sample of 1332 non-psychiatric offenders, brain-age measures using patterns of gray matter volume derived from independent component analyses incrementally added to Go-NoGo related ACC activity and psychopathy scores in predicting antisocial behavior (Kiehl et al., 2018). These results indicate abnormal neural error-processing and structural brain-age to have predictive value above already established factors when estimating recidivism in non-psychiatric populations (Kiehl et al., 2018; Steele et al., 2015).

One exploratory imaging study investigating neuroprediction was conducted in forensic psychiatry (Tortora et al., 2020). In a small sample of 44 patients, the majority (68%) of whom were diagnosed with psychotic disorders, the inclusion of resting-state regional cerebral blood

flow measured by single-photon emission computed tomography resulted in improved general recidivism risk prediction above traditional factors (Delfin et al., 2019). Lower blood flow in the parietal lobe was observed to be the strongest predictor during a 10-year average follow-up, with lower temporal and higher cerebellar activity partially contributing to model accuracy (Delfin et al., 2019). These preliminary results suggest multivariate neuroimaging techniques to incrementally add to risk assessment performance in forensic patients as well.

Multivariate algorithms and biomarker/neuroprediction appear to promise improved risk estimates of aggression and crime beyond current methods used in psychiatry (Gou et al., 2021; Tortora et al., 2020). The main constraint remains the amount of neuroimaging data available for studying aggression in schizophrenia (Fjellvang et al., 2018). The remarkable undertaking by Kiehl et al. (2018) proves the feasibility of acquiring the quantity necessary for neuropredictive purposes in a forensic setting, albeit at the disadvantage of significant financial investments and technical challenges. In lieu of this, data-sharing between research groups could facilitate attaining the numbers required and would entail standardizing data and clinical classification across samples (Arbabshirani et al., 2017).

Risk assessment algorithms are employed in certain criminal justice systems for the purposes of evaluation and sentencing (Kehl, Guo & Kessler, 2017). Categorization based on such tools remain imperfect and carry the potential for unwarranted detention and stigmatization (Large et al., 2011). Current algorithms have further been criticized for including variables such as socioeconomic status and education which can exacerbate prejudice against populations already experiencing discrimination (Kehl et al., 2017; Monahan & Skeem, 2016). Instruments guiding judicial decision-making should be free of predictive biases (Monahan & Skeem, 2016) and biomarkers (e.g., genetics, neuroimaging) could in theory offer unbiased factors to inform

prognostication (Tortora et al., 2020). However, this might imply that crime and violence can be reduced to a brain problem, thereby limiting or omitting the known contribution of individual, social, and situational factors to the emergence of aggression (Gkotsi & Gasser, 2016). Offender who suffered brain damage might also be rendered more susceptible to stigmatization (Fazel et al., 2011; Gkotsi & Gasser, 2016). Furthermore, the advent of highly accurate assessments owing to the combination of machine learning and neurosciences could introduce a novel form of determinism in the legal system (Tortora et al., 2020). Biomarkers in risk assessment tools have the potential to solve certain limitations of the current instruments and raise new ethical issues which need addressing to avoid incorporating neuro-makers in judicial decision processes prematurely (Greely et al., 2018).

In summary, the integration of task-based functional neuroimaging assessing cognitive control in predictive models of recidivism by Aharoni et al. (2013) and Kiehl et al. (2018) further lends supports to research efforts such as ours. It demonstrates that risk prognostication can benefit from the investigation of specific neural mechanisms underlying aggression in individuals with schizophrenia. Future neuroprediction studies should contemplate examining negative emotion processing (Tikàsz et al., 2020; Tikasz et al., 2016) and affective-inhibitory control (Tikasz et al., 2017) as incremental neurocognitive risk factors for aggression in schizophrenia.

# 7 Conclusion

In the current study, we used task-based functional magnetic resonance imaging to investigate emotional processing, cognitive control, and reward processing in individuals with schizophrenia with a history of aggressive behaviors. This is the first study to identify functional brain activity and connectivity during the processing of negative emotions specific to aggressive men with schizophrenia. This is also the first study to observe the neural mechanisms involved in the interaction between cognitive control and anger processing among violent men with schizophrenia. We did not, however, observe a relation between the reward-reinforcing system and aggression. Our results directly contribute to the literature by providing neural bases for the impaired interaction between cognitive control and emotion regulation observed in violent individuals with schizophrenia. Understanding the neurobiology of aggression in schizophrenia is important for improving prevention, treatment, risk assessment, and prognostication (Lamsma & Harte, 2015; Rosell & Siever, 2015). Our results should encourage therapeutic efforts to remediate cognitive impairments as well as the future use of neuroprediction in aggressive individuals with schizophrenia.

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